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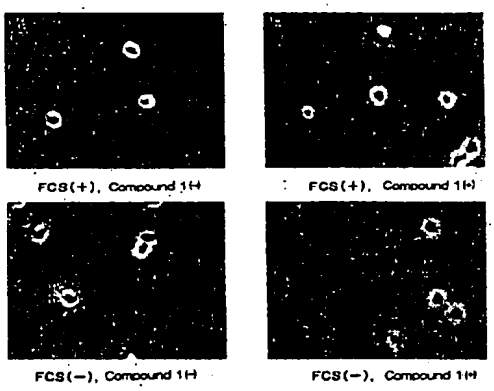
(54) VISUAL FUNCTION IMPROVING AGENTS

(57) The present invention provides a visual function disorder improving agent containing a compound having Rho kinase inhibitory activity, particularly (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, as an effective component. This agent has axon of the retinal ganglion cellal extension promoting action and optic nerve cell regeneration promoting action, and is useful for the treatment of a visual function disorder associated with various eye diseases caused by damage, defects, degeneration and the like in the retinal or optic nerve.

FIG. 1



EP 1 378 247 A1

Description

Technical Field

[0001] The present invention relates to a visual function disorder improving agent containing a compound having Rho kinase inhibitory activity.

Background Of The Invention

[0002] The retinal ganglion cell is a retinal output cell, and its axon is also called an optic nerve fibers, runs in the retinal inner layer and the nerve fibers layer (nearest side to the vitreous body), gathers at the optic disc, leaves the eye ball, forms an optic nerve and undertakes a role of transmitting visual information to the cerebral cortex. Moreover, the retinal ganglion cell is distributed over the entire area of the retina. Accordingly, for example, a retinal damage due to inflammation and the like causes retinal neuropathy, retinal vascular occlusion, periphlebitis retinae, Eales' disease, ischemic ophthalmopathy, retinal arteriolar microaneurysm, retinopathy caused by hypertension, renal disease and blood disease, diabetic retinopathy, retinal dystrophy, macular dystrophy, chorioretinopathy, macular degeneration, macular edema, retinal pigment epithelium detachment, degenerative retinoschisis, retinoblastoma, retinal pigment epithelioma and the like, along with which a visual disorder occurs. Furthermore, degeneration and damage of the optic nerve causes the onset of optic neuritis, capillary angioma of optic disc, ischemic optic neuropathy, defects of retinal nerve fibers layer, retinal optic atrophy, neurotmesis of optic nerve, traumatic optic neuropathy, choked disc, coloboma of optic disc, optic nerve hypoplasia, toxic optic atrophy and the like, along with which a visual disorder occurs. It is further known that elevated intraocular pressure (glaucoma etc.) and the like cause atrophy and degeneration of the optic nerve, which in turn causes a visual disorder. For these visual disorders, a pharmaceutical agent capable of recovering the function of the visual information transmission pathway in the retina, particularly a pharmaceutical agent capable of neogenesis (regeneration) of the axon of retinal ganglion cell and promotion of extension thereof, and a pharmaceutical agent capable of neogenesis (regeneration) of the optic nerve cell are considered to be useful. While surgical efforts have been made in recent years such as retinal transplantation and retinal regeneration, in such efforts, too, it is highly useful to find a means and a pharmaceutical agent to promote neogenesis (regeneration) and extension of the optic nerve axon after transplantation.

[0003] On the other hand, as a compound having a Rho kinase inhibitory activity, a compound of the formula (I) to be mentioned later has been reported recently [WO98/06433 (corresponding patents: EP956865 and US6218410)]. Certain isoquinolinesulfonamide derivative and isoquinoline derivative are also reported to show a Rho kinase inhibitory activity (WO98/06433 and Naunyn-Schmiedeberg's Archives of Pharmacology 385(1) Suppl., R219, 1998). Furthermore, it has been reported that ethacrynic acid, certain vinyl benzene derivatives such as 4-[2-(2,3,4,5,6-pentafluorophenyl)-acryloyl]cinnamic acid and the like have a Rho kinase inhibitory activity [WO00/57914, JP-A-2000-44513 (corresponding patents: EP1094055 and US6329547)]. In addition, it has been reported that certain kinds of nitrogen-containing compounds, inclusive of N-[1-(3,5-dimethoxybenzyl)-tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine, have Rho kinase inhibitory activity (WO01/56988). It has been also reported that certain kinds of thiochroman compounds have Rho kinase inhibitory activity (WO01/68607).

[0004] The Rho kinase is a serin/threonine kinase activated along with the activation of Rho, and is known to function at the downstream of Rho and phosphorylate various substances, thereby controlling various physiological functions such as formation of stress fibers and desmosomes, contraction of smooth muscle, retraction of nerve axon and the like.

[0005] Inhibition of Rho kinase having such various physiological functions is considered to lead to the prophylaxis or treatment of various disease states, diseases and disorders. For example, as a pharmaceutical use of a compound having Rho kinase inhibitory activity, WO98/06433 widely discloses a therapeutic agent of hypertension, a therapeutic agent of angina pectoris, a cerebrovascular spasm suppressant, a therapeutic agent of asthma, a therapeutic agent of peripheral circulatory disturbance, a premature delivery preventive, a therapeutic agent of arterial sclerosis, an anticancer drug, an antiinflammatory agent, an immunosuppressant, a therapeutic agent of autoimmune diseases, an anti-AIDS agent, a therapeutic agent of osteoporosis, a therapeutic agent of retinopathy, a cerebral function improver, a contraceptive drug, and a gastrointestinal tract infection preventive. In addition, WO01/56988 published after the earliest priority date of the present application describes that a specific compound having Rho kinase inhibitory activity is useful as a therapeutic agent of hypertension, asthma, angina pectoris, cerebrovascular contraction, peripheral circulation disorder, threatened abortion, glaucoma, tunnel vision, frequent urination, cancer, infiltration and metastasis of cancer, arteriosclerosis, retinopathy, immune response, inflammatory autoimmune disease, cerebral function disorder, osteoporosis, bacterial infection, chronic kidney failure, chronic nephritis, diabetic nephropathy, IgA nephropathy, a disease relating to the formation of thrombus, rheumatism, erectile dysfunction and fibrosis. Since it also has intraocular pressure lowering action, optic disc blood flow increasing action and aqueous humor outflow promoting action based on cilliary muscle relaxing action, its use as an agent for the prophylaxis or therapy of glaucoma has been

reported [WO00/09162 (corresponding to EP1034793)]. WO00/57914 also describes its usefulness as an intraocular pressure lowering agent.

[0006] Furthermore, the compound of formula (I) has been already known to be useful as an agent for the prophylaxis or treatment of disorders of circulatory organs such as coronary, cerebral, renal, peripheral artery and th like (e.g., a therap utic agent of hypertension, a therapeutic agent of angina pectoris, a therapeutic agent of renal and peripheral circulation disorder, a suppressive agent of cerebrovascular contraction and the like), which is potent and long lasting, and also as a therapeutic agent of asthma [JP-A-62-89679, JP-A-3-218356, JP-A-4-273821, JP-A-5-194401 (corresponding patents; EP641781 and US5478838), JP-A-6-41080 and WO95/28387 (corresponding patents; EP757038, US5958944 and US6156766)].

[0007] The isoquinolinesulfonamide derivative described in the above-mentioned WO98/06433 is known to be effective as a vasodilating agent, a therapeutic agent of hypertension, a cerebral function improver, an anti-asthma agent, a heart protecting agent, a platelet aggregation inhibitor, a therapeutic agent of neurologic manifestation, an antiinflammatory agent, an agent for the prevention and treatment of hyperviscosity syndrome, a therapeutic agent of glaucoma, an intraocular pressure lowering agent, an improver of motor paralysis due to of cerebral thrombosis, an agent for prevention and treatment of virus infection and transcriptional control factor inhibitor [JP-A-57-200366, JP-A-61-227581, JP-A-2-256617, JP-A-4-264030, JP-A-6-56668 (corresponding patents; EP654266 and US5747507), JP-A-6-80569 (corresponding patent; WO94/05290), JP-A-6-293643, JP-A-7-41424, JP-A-7-277979, WO97/23222 (corresponding patents; EP868186 and US6271224), JP-A-9-227381, JP-A-10-45598 and JP-A-10-87491].

[0008] Moreover, the isoquinoline derivative described in the above-mentioned publication (Naunyn-Schmiedeberg's Archives of Pharmacology 385(1) Suppl., R219, 1998) is known to be useful as an agent for the prevention and treatment of brain tissue disorder due to vasospasm [WO97/28130 (corresponding patents; EP885888 and US6153608)].

[0009] However, there is no description disclosing that a compound having Rho kinase inhibitory activity has an action to improve visual function disorder or an action to improve visual function disorder caused by damage and/or degeneration of retinal nerve cell (the neural retina) or optic nerve (the nervus opticus), particularly an action to promote regeneration and extension of the axon of retinal ganglion cell.

[0010] The Rho-Rho kinase pathway is known to exhibit various functions in living organism as mentioned above, and involvement in the extension of nerve axon has been recently reported (The Journal of Cell Biology, vol. 141, 1625-1636 (1998), Neuron, 26, 431-441 (2000), The Journal of Neuroscience, vol. 19(17), 7537-7547 (1999)). However, none of them directly teaches the role of Rho kinase in retinal ganglion cell or the effect afforded by a Rho kinase inhibitor, and there is no description to suggest the usefulness of the Rho kinase inhibitor in the recovery of the visual function.

Disclosure of the Invention

[0011] An object of the present invention is to provide a novel visual function disorder improving agent useful for recovery of the visual function impaired due to damage and/or degeneration of the retinal nerve cell or optic nerve. The present invention aims at provision of a pharmaceutical agent useful for neogenesis, extension and promotion of extension of the axon of a retinal ganglion cell, as well as regeneration of an optic nerve cell.

[0012] The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a compound having Rho kinase inhibitory activity has an action of neogenesis, extension and promotion of extension of axon of a retinal ganglion cell, as well as an optic nerve cell regenerating action, and therefore found that the compound is useful for the recovery of the visual function impaired due to damage and/or degeneration of the retinal nerve cell or optic nerve, which resulted in the completion of the present invention.

[0013] Accordingly, the present invention provides the following.

(1) A visual function disorder improving agent that improves a visual function disorder caused by damage or degeneration of retinal nerve cell or optic nerve, which contains a compound having Rho kinase inhibitory activity.

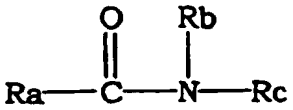
(2) The visual function disorder improving agent of the above-mentioned (1), wherein the improvement of the visual function disorder is by way of promotion of extension of axon of a retinal ganglion cell.

(3) The visual function disorder improving agent of the above-mentioned (1), wherein the improvement of the visual function disorder is by way of regeneration of the optic nerve cell.

(4) An agent for promoting extension of axon of a retinal ganglion cell, which comprises a compound having Rho kinase inhibitory activity as an effective component.

(5) An agent for promoting regeneration of an optic nerve cell, which comprises a compound having Rho kinase inhibitory activity as an effective component.

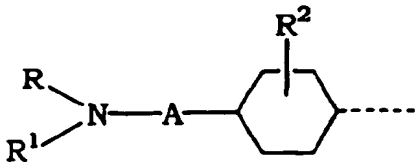
(6) The agent of any of (1) to (5) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



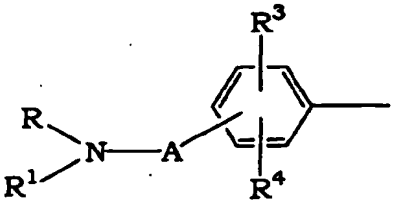
(I)

wherein

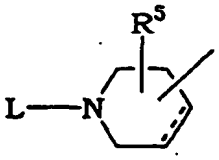
Ra is a group of the formula



(a)



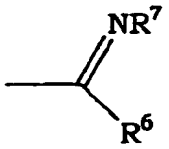
(b)



(c)

in the formulas (a) and (b),

R is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



(d)

wherein R^6 is hydrogen, alkyl or formula: $-NR^8R^9$ wherein R^8 and R^9 are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R^7 is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R^6 and R^7 in combination show a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

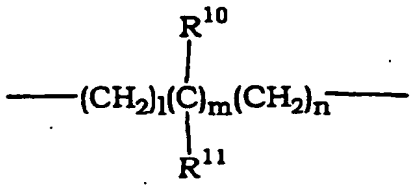
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,

or R and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl or azide, and

A is a group of the formula

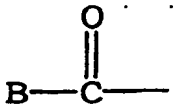


(e)

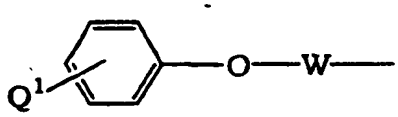
wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

in the formula (c) ,

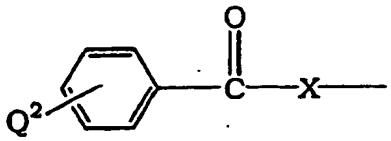
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



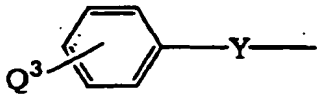
(f)



(g)



(h)



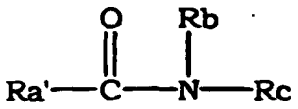
(i)

wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,
Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,
W is alkylene,
Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,
X is alkylene,
Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;
and Y is a single bond, alkylene or alkenylene, and

in the formula (c) ,
a bond denoted by a broken line and a solid line

is a single bond or a double bond;
R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

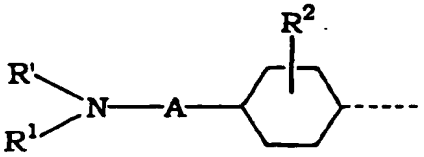
an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.
(7) The agent of any of (1) to (5) above, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



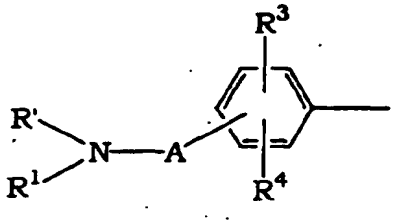
(I')

wherein

Ra' is a group of the formula



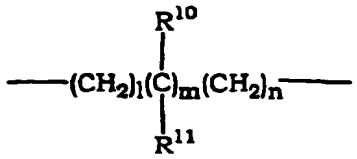
(a')



(b')

wherein

R'	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,
R^1	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or
R' and R^1	in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,
R^2	is hydrogen or alkyl,
R^3 and R^4	are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and
A	is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb	is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc	is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt th r of, or a prodrug thereof.

(8) The ag nt of any of (1) to (5) above, wh rein the compound having a Rho kinase inhibitory activity is (R)-(+)

-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof, especially (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamid monohydrochloride.

(9) The agent of any of (1) to (5) above, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid or a pharmaceutically acceptable salt thereof.

(10) A pharmaceutical composition for improving a visual function disorder, which comprises a compound having Rho kinase inhibitory activity and a carrier acceptable for formulation of a preparation, which improves a visual function disorder caused by damage or degeneration of retinal nerve cell or optic nerve.

(11) The pharmaceutical composition for improving visual function disorder of the above-mentioned (10), wherein the improvement of the visual function disorder is by way of promotion of extension of axon of a retinal ganglion cell.

(12) The pharmaceutical composition for improving visual function disorder of the above-mentioned (10), wherein the improvement of the visual function disorder is by way of regeneration of an optic nerve cell.

(13) A pharmaceutical composition for promoting extension of axon of a retinal ganglion cell, which comprises a compound having Rho kinase inhibitory activity and a carrier acceptable for formulation of a preparation.

(14) A pharmaceutical composition for promoting regeneration of an optic nerve cell, which comprises a compound having Rho kinase inhibitory activity and a carrier acceptable for formulation of a preparation.

(15) The pharmaceutical composition of any of the above-mentioned (10)-(14), wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the above-mentioned formula (I), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

(16) The pharmaceutical composition of any of the above-mentioned (10)-(14), wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the above-mentioned formula (I'), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

(17) The pharmaceutical composition of any of the above-mentioned (10)-(14), wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof, particularly (R) - (+) -N- (1H-pyrrolo[2,3-b]pyridin-4-yl) -4- (1-aminoethyl)benzamide monohydrochloride.

(18) The pharmaceutical composition of any of the above-mentioned (10)-(14), wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid or a pharmaceutically acceptable salt thereof.

(19) A method of improving a visual function disorder caused by damage or degeneration of a retinal nerve cell or an optic nerve, which comprises administering an effective amount of a compound having Rho kinase inhibitory activity to a patient.

(20) The method of the above-mentioned (19), wherein the improvement of the visual function disorder is by way of promotion of extension of axon of a retinal ganglion cell.

(21) The method of the above-mentioned (19), wherein the improvement of the visual function disorder is by way of regeneration of an optic nerve cell.

(22) A method of promoting extension of axon of a retinal ganglion cell, which comprises administering an effective amount of a compound having Rho kinase inhibitory activity to a patient.

(23) A method of promoting regeneration of an optic nerve cell, which comprises administering an effective amount of a compound having Rho kinase inhibitory activity to a patient.

(24) The method of any of the above-mentioned (19)-(23), wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the above-mentioned formula (I), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

(25) The method of any of the above-mentioned (19)-(23), wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the above-mentioned formula (I'), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

(26) The method of any of the above-mentioned (19)-(23), wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof, particularly (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

(27) The method of any of the above-mentioned (19)-(23), wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid or a pharmaceutically acceptable salt thereof.

(28) Use of a compound having Rho kinase inhibitory activity for the production of an agent for improving a visual function disorder, which improves a visual function disorder caused by damage or degeneration of retinal nerve cell or optic nerve.

(29) Use of the abov -mentioned (28), wherein the improvement of the visual function disorder is by way of pro-

motion of extension of axon of a retinal ganglion cell.

(30) Use of the above-mentioned (28), wherein the improvement of the visual function disorder is by way of regeneration of an optic nerve cell.

(31) Use of a compound having Rho kinase inhibitory activity for the production of an agent for promoting extension of axon of a retinal ganglion cell.

(32) Use of a compound having Rho kinase inhibitory activity for the production of an agent for promoting the regeneration of an optic nerve cell.

(33) The use of any of the above-mentioned (28) - (32), wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the above-mentioned formula (I), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

(34) The use of any of the above-mentioned (28)-(32), wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the above-mentioned formula (I'), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

(35) The use of any of the above-mentioned (28)-(32), wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof, particularly (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

(36) The use of any of the above-mentioned (28)-(32), wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid or a pharmaceutically acceptable salt thereof.

[0014] In addition, with regard to the visual function impaired due to damage and/or degeneration of retinal nerve cell or optic nerve, the present invention provides a method for improving a visual function, use of a compound having Rho kinase inhibitory action for the production of a pharmaceutical agent to improve visual function, a composition for improving visual function and a commercial package containing a composition for improving visual function.

Brief Description of the Drawings

[0015] In the Figures , compound 1 means (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide dihydrochloride 3/2 hydrate, compound 2 means (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride, compound 3 means 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid, compound 4 means ethacrynic acid, and compound 5 means fasudil hydrochloride.

[0016] Fig. 1 shows a microscopic image indicating the level of extension of the nerve axon of retinal ganglion cell in the presence or absence of a Rho kinase inhibitor (compound 1), wherein A shows an image with the addition of fetal calf serum (FCS) and without addition of a Rho kinase inhibitor, B shows an image with the addition of FCS and a Rho kinase inhibitor, C shows an image without the addition of FCS and a Rho kinase inhibitor, and D shows an image without addition of FCS and with the addition of a Rho kinase inhibitor.

[0017] Fig. 2 is a graph showing the measurement results of the level of regeneration of an optic nerve cell in rats, on which the optic nerve was cut off and the sciatic nerve was auto-transplanted, wherein the vertical axis shows the proportion of the regenerated optic nerve cells per 1 mm^2 relative to the control group, which was measured both when a Rho kinase inhibitor (compound 1) was and was not added.

[0018] Fig. 3 shows a microscopic image indicating the level of extension of the nerve axon of retinal ganglion cell in the presence or absence of a Rho kinase inhibitor (compound 2), wherein A shows an image of culture in a culture medium with the addition of FCS, B shows an image of culture in a culture medium without the addition of FCS, C shows an image of culture in a medium without the addition of FCS and then with the addition of a Rho kinase inhibitor, and D shows an image of culture in a medium without addition of FCS and then with the addition of LPA, which is a Rho activator.

[0019] Fig. 4 shows images under microscope (fluorescence microscope) showing the measured results by retrograde labeling of the regenerated optic nerve cell in rats, on which the optic nerve was cut off and the sciatic nerve was auto-transplanted, wherein A shows the labeled optic nerve cell of rats (normal group) free of transplantation, B shows labeled regenerated optic nerve cell in the absence of a Rho kinase inhibitor after cutting off the optic nerve of the rats and auto-transplanting the sciatic nerve (control group), C shows labeled optic nerve cell in the presence of a Rho kinase inhibitor after cutting off the optic nerve of the rats and auto-transplanting the sciatic nerve (compound 2 treatment group-1).

[0020] Fig. 5 is a graph showing the measurement results of the level of regeneration of an optic nerve cell in rats, on which the optic nerve was cut off and the sciatic nerve was auto-transplanted, wherein the vertical axis shows the proportion of the regenerated optic nerve cells per 1 mm^2 relative to the normal group.

[0021] Fig. 6 is a graph showing the influence of various Rho kinase inhibitors (compound 3, compound 4 and com-

pound 5) on extension of axon of a retinal ganglion cell, wherein th vertical axis shows th proportion of axon extended cell count relative to the r tinal ganglion cell count. In the Figur , the results with * indicate a significant differenc ($p<0.05$) from the control.

Detailed Descripti n of th Inv nti n

[0022] The visual function disorder in the present invention means a visual disorder or a disease with various symptoms of loss of vision, low vision, narrow vision, abnormal color sensation and misty vision, abnormal electroretinogram, and visually evoked potential and the like, which is caused by decreased retinal ganglion cells and optic nerve fibers due to damage, degeneration, and the like, of retinal nerve or optic nerve, optic atrophy, loss of nerve fibers axon, nerve fibers demyelination of optic nerve or defects of optic nerve, and which is specifically exemplified by a visual disorder accompanying damage due to retinal inflammation and the like (retinal neuropathy, retinal vascular occlusion, periphlebitis retinae, Eales' disease, ischemic ophthalmopathy, retinal arteriolar microaneurysm, retinopathy caused by hypertension, renal disease and blood disease, diabetic retinopathy, retinal dystrophy, macular dystrophy, chorioretinopathy, macular degeneration, macular edema, retinal pigment epithelium detachment, degenerative retinoschisis, retinoblastoma, retinal pigment epithelioma etc.) and the like; a visual disorder accompanying degeneration or damage of optic nerve (optic neuritis, capillary angioma of optic disc, ischemic optic neuropathy, defects of retinal nerve fibers layer, retinal optic atrophy, neurotmesis of optic nerve, traumatic optic neuropathy, choked disc, coloboma of optic disc, optic nerve hypoplasia, toxic optic atrophy etc.); visual disorder due to optic atrophy, degeneration and the like caused by elevated intraocular pressure (glaucoma etc.) and the like; and the like.

[0023] In the present invention, improvement of visual function disorder is intended to mean improving a visual disorder caused by damage, degeneration and the like of retinal nerve and optic nerve, by extension or promotion of extension of axon of a retinal ganglion cell, regeneration of optic nerve cell and the like. In addition, the present invention aims at providing a pharmaceutical agent having a promoting action on the extension of axon of a retinal ganglion cell and/or regenerative action of an optic nerve cell, and such pharmaceutical agent is also encompassed in the scope of the present invention.

[0024] Here, in the present invention, the "promotion of extension of axon" encompasses any state where the growth of axon is observed, such as neogenesis (regeneration), extension and the like of the axon in the earlier stages, not to mention the action of promotion of extension of axon of a retinal ganglion cell, namely, an action to elongate the axon and to form synapse. Therefore, even when simply referred with "an agent for promoting extension of axon" or "promotion of extension of axon" in the present specification, the agent means any agent that activates or induces neogenesis (regeneration), extension, promotion of extension and the like of the axon of retinal ganglion cell. Furthermore, by the neogenesis (regeneration) action of the optic nerve cell is meant an increase in the number of the optic nerve cells that have been retrogradely degenerated or decreased due to damage, degeneration and the like of the axon and by the "agent for promoting neogenesis of the optic nerve cell" is meant any agent that promotes an increase in the number of the regenerated optic nerve cells.

[0025] The compound having a Rho kinase inhibitory activity, which is used as an active ingredient in the present invention, may be any as long as it has a Rho kinase inhibitory activity. In the present invention, Rho kinase means serine/threonine kinase activated along with the activation of Rho. For example, ROK_{α} (ROCKII: Leung, T. et al, J. Biol. Chem., 270, 29051-29054, 1995), p160 ROCK (ROKβ, ROCK-I: Ishizaki, T. et al, The EMBO J., 15(8), pp. 1885-1893, 1996) and other proteins having a serine/threonine kinase activity are exemplified.

[0026] Examples of the compound having a Rho kinase inhibitory activity, which is used in the present invention, include the amide compound, isoquinolinesulfonamide derivative and isoquinoline derivative described in the above-mentioned WO98/06433, WO97/28130 and Naunyn-Schmiedeberg's Archives of Pharmacology 385(1), Suppl., R219 (1998), and vinyl benzene derivative and ethacrynic acid described in WO00/57914 and JP-A-2000-44513. In addition, the nitrogen-containing compound described in WO01/56988 can be also mentioned. Furthermore, the thiochroman compounds described in WO01/68607 can be mentioned.

[0027] As the aforementioned amide compound, for example, a compound of the above-mentioned formula (I), particularly a compound of the formula (I'), are used. As the aforementioned isoquinolinesulfonamide derivative, hexahydro-1-(5-isoquinolinesulfonyl)-1H-1,4-diazepine hydrochloride [fasudil hydrochloride] and the like are used. As the aforementioned isoquinoline derivative, hexahydro-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine dihydrochloride, (S)-(+)-hexahydro-2-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride, hexahydro-7-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine dihydrochloride, hexahydro-5-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine dihydrochloride, hexahydro-2-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride, (R)-(-)-hexahydro-2-methyl-1-[(4-methyl-5-isoquinolinyl)-sulfonyl]-1H-1,4-diazepine hydrochloride, (R)-(+)-hexahydro-5-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride and the like are used.

[0028] As the aforementioned vinyl benzene derivative, 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid and

th lik are mentioned. As the aforementioned nitrogen-containing compound, N-[1-(3,5-dimethoxybenzyl)t trahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine and the like can be mentioned.

[0029] Preferred are the amide compound repr sented by th formula (I), isoquinolinesulfonamide d rivativ , vinylbenzene d rivative and ethacrynic acid, and particularly pref rr d are the amide compound repres nted by the formula (I'), fasudil hydrochloride, ethacrynic acid and 4-[2-(2,3,4,5,6-p ntafluoroph nyl)acryloyl]cinnamic acid.

[0030] Further, as the aforementioned thiochroman compounds, the following compounds can be mentioned:

(S)-4-amino-N-(4-pyridyl)thiochroman-7-carboxamide,
(S)-4-amino-N-(4-pyridyl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)thiochroman-7-carboxamide,
(S)-4-amino-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiochroman-7-carboxamide,
(S)-4-amino-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-6-methyl-N-(4-pyridyl)thiochroman-7-carboxamide,
(S)-4-amino-6-methyl-N-(4-pyridyl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-6-chloro-N-(4-pyridyl)thiochroman-7-carboxamide,
(S)-4-amino-6-chloro-N-(4-pyridyl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-8-methyl-N-(4-pyridyl)thiochroman-7-carboxamide,
(S)-4-amino-8-methyl-N-(4-pyridyl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-6-methyl-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiochroman-7-carboxamide 1,1-dioxide,
(S)-4-amino-6-chloro-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiochroman-7-carboxamide 1,1-dioxide

[0031] In the present invention, one kind of a compound having a Rho kinase inhibitory activity may be used alone, or, where necessary, several kinds may be concurrently used.

[0032] In the present invention, moreover, a compound having Rho kinase inhibitory activity, which is an effective component, and other visual function disorder improving agents can be used in combination.

[0033] In the present specification, each symbol of the formulas (I) and (I') is defined as follows.

[0034] Alkyl for R, R' and R^1 is linear or branched alkyl having 1 to 10 carbon atoms, which is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and the like, with preference given to alkyl having 1 to 4 carbon atoms.

[0035] Cycloalkyl for R, R' and R^1 has 3 to 7 carbon atoms and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

[0036] Cycloalkylalkyl for R, R' and R^1 is that wherein the cycloalkyl moiety is the above-mentioned cycloalkyl having 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like), which is exemplified by cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylpropyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl, cyclopropylbutyl, cyclobutylbutyl, cyclopentylbutyl, cyclohexylbutyl, cycloheptylbutyl, cyclopropylhexyl, cyclobutylhexyl, cyclopentylhexyl, cyclohexylhexyl, cycloheptylhexyl and the like.

[0037] Aralkyl for R, R' and R^1 is that wherein alkyl moiety is alkyl having 1 to 4 carbon atoms and is exemplified by phenylalkyl such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl and the like.

[0038] The substituent of optionally substituted cycloalkyl, cycloalkylalkyl, phenyl and aralkyl on the ring for R, R' and R^1 is halogen (e.g., chlorine, bromine, fluorine and iodine), alkyl (same as alkyl for R, R' and R^1), alkoxy (linear or branched alkoxy having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy and the like), aralkyl (same as aralkyl for R, R' and R^1) or haloalkyl (alkyl for R, R' and R^1 which is substituted by 1-5 halogen, and exemplified by fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl and the like), nitro, amino, cyano, azide and the like.

[0039] The group formed by R and R^1 or R' and R^1 in combination together with the adjacent nitrogen atom, which forms a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom is preferably a 5 or 6-membered ring and condensed ring thereof. Examples thereof include 1-pyrrolidinyl, piperidino, 1-piperazinyl, morpholino, thiomorpholino, 1-imidazolyl, 2,3-dihydrothiazol-3-yl and the like. The substituent of the optionally substituted nitrogen atom is exemplified by alkyl, aralkyl, haloalkyl and the like. As used herein, alkyl, aralkyl and haloalkyl are as defined for R, R' and R^1.

[0040] Alkyl at R^2 is as defined for R, R' and R^1.

[0041] Halogen, alkyl, alkoxy and aralkyl at R^3 and R^4 are as defined for R, R' and R^1.

[0042] Acyl at R^3 and R^4 is alkanoyl having 2 to 6 carbon atoms (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl and the like), benzoyl or phenylalkanoyl wherein th alkanoyl moiety has 2 to 4 carbon atoms (e.g., ph nylacetyl, phenylpropionyl, phenylbutyryl and the like).

[0043] Alkylamino at R^3 and R^4 is that wherein th alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms. Examples thereof include methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, tert-butylamino, pentylamino, hexylamino and the lik .

[0044] Acylamino at R^3 and R^4 is that wherein acyl moiety is alkanoyl having 2 to 6 carbon atoms, benzoyl or the alkanoyl moiety is phenylalkanoyl having 2 to 4 carbon atoms and the like, which is exemplified by acetylamino, propionylamino, butyrylamino, valerylamino, pivaloylamino, benzoylamino, phenylacetylamino, phenylpropionylamino, phenylbutyrylamino and the like.

[0045] Alkylthio at R^3 and R^4 is that wherein the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms, which is exemplified by methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, hexylthio and the like.

[0046] Aralkyloxy at R^3 and R^4 is that wherein the aralkyl moiety is aralkyl having C_{1-4} alkyl, which is exemplified by benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy and the like.

[0047] Aralkylthio at R^3 and R^4 is that wherein the aralkyl moiety is aralkyl having C_{1-4} alkyl, which is exemplified by benzylthio, 1-phenylethylthio, 2-phenylethylthio, 3-phenylpropylthio, 4-phenylbutylthio and the like.

[0048] Alkoxycarbonyl at R^3 and R^4 is that wherein the alkoxy moiety is linear or branched alkoxy having 1 to 6 carbon atoms, which is exemplified by methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl and the like.

[0049] Mono- or di-alkylcarbamoyl at R^3 and R^4 is carbamoyl mono- or di-substituted by alkyl having 1 to 4 carbon atoms, which is exemplified by methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, dipropylcarbamoyl, butylcarbamoyl, dibutylcarbamoyl and the like.

[0050] Alkoxy at R^5 is as defined for R, R' and R^1.

[0051] Alkoxycarbonyloxy at R^5 is that wherein the alkoxy moiety is linear or branched alkoxy having 1 to 6 carbon atoms, which is exemplified by methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, sec-butoxycarbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyloxy and the like.

[0052] Alkanoyloxy at R^5 is that wherein the alkanoyl moiety is alkanoyl having 2 to 6 carbon atoms, which is exemplified by acetyloxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy and the like.

[0053] Aralkyloxycarbonyloxy at R^5 is that wherein the aralkyl moiety is aralkyl having C_1-C_4 alkyl, which is exemplified by benzyloxycarbonyloxy, 1-phenylethyloxycarbonyloxy, 2-phenylethyloxycarbonyloxy, 3-phenylpropyloxycarbonyloxy, 4-phenylbutyloxycarbonyloxy and the like.

[0054] Alkyl for R^6 is as defined for R, R' and R^1; alkyl for R^8 and R^9 is as defined for R, R' and R^1; and aralkyl for R^8 and R^9 is as defined for R, R' and R^1.

[0055] Alkyl for R^7 is as defined for R, R' and R^1 and aralkyl for R^7 is as defined for R, R' and R^1.

[0056] The group formed by R^6 and R^7 in combination, which forms a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom, is exemplified by imidazol-2-yl, thiazol-2-yl, oxazol-2-yl, imidazolin-2-yl, 3,4,5,6-tetrahydropyridin-2-yl, 3,4,5,6-tetrahydropyrimidin-2-yl, 1,3-oxazolin-2-yl, 1,3-thiazolin-2-yl or optionally substituted benzoimidazol-2-yl, benzothiazol-2-yl, benzoxazol-2-yl and the like having a substituent such as halogen, alkyl, alkoxy, haloalkyl, nitro, amino, phenyl, aralkyl and the like. As used herein, halogen, alkyl, alkoxy, haloalkyl and aralkyl are as defined for R, R' and R^1.

[0057] The substituent of the above-mentioned optionally substituted nitrogen atom is exemplified by alkyl, aralkyl, haloalkyl and the like. As used herein, alkyl, aralkyl and haloalkyl are as defined for R, R' and R^1.

[0058] Hydroxyalkyl for R^{10} and R^{11} is linear or branched alkyl having 1 to 6 carbon atoms which is substituted by 1 to 3 hydroxy, which is exemplified by hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and the like.

[0059] Alkyl for R^{10} and R^{11} is as defined for R, R' and R^1; haloalkyl and alkoxycarbonyl for R^{10} and R^{11} are as defined for R, R' and R^1; aralkyl for R^{10} and R^{11} is as defined for R, R' and R^1.

[0060] Cycloalkyl formed by R^{10} and R^{11} in combination is the same as cycloalkyl for R, R' and R^1.

[0061] Alkyl for L is as defined for R, R' and R^1.

[0062] Aminoalky for L is a linear or branched alkyl having 1 to 6 carbon atoms, which is substituted by amino, which is exemplified by aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, 6-aminohexyl and the like.

[0063] Mono- or dialkylaminoalkyl for L is mono- or di-substituted aminoalkyl with alkyl having 1 to 4 carbon atoms, which is exemplified by methylaminomethyl, dimethylaminomethyl, ethylaminomethyl, diethylaminomethyl, propylaminomethyl, dipropylaminomethyl, butylaminomethyl, dibutylaminomethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl and the like.

[0064] Carbamoylalkyl for L is linear or branched alkyl having 1 to 6 carbon atoms substituted by carbamoyl, which is exemplified by carbamoylmethyl, 2-carbamoylethyl, 1-carbamoylethyl, 3-carbamoylpropyl, 4-carbamoylbutyl, 5-car-

barnoylpentyl, 6-carbamoylhexyl and the like.

[0065] Phthalimidoalkyl for L is linear or branch d alkyl having 1 to 6 carbon atoms, which is substituted by phthalimid . Exampl s thereof include phthalimidomethyl, 2-phthalimidoethyl, 1-phthalimidoethyl, 3-phthalimidopropyl, 4-phthalimidobutyl, 5-phthalimidop ntyl, 6-phthalimidohexyl and th like.

[0066] Alkyl for B is as defined for R, R' and R^1.

[0067] Alkoxy for B is as defined for R, R' and R^1.

[0068] Aralkyl for B is as defined for R, R' and R^1.

[0069] Aralkyloxy for B is as defined for R^3 and R^4.

[0070] Aminoalkyl for B is as defined for L.

[0071] Hydroxyalkyl for B is as defined for R^{10} and R^{11}.

[0072] Alkanoyloxyalkyl for B is that wherein linear or branched alkyl having 1 to 6 carbon atoms is substituted by alkanoyloxy having alkanoyl moiety having 2 to 6 carbon atoms, which is exemplified by acetyloxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, acetyloxyethyl, propionyloxyethyl, butyryloxyethyl, valeryloxyethyl, pivaloyloxyethyl and the like.

[0073] Alkoxycarbonylalkyl for B is that wherein linear or branched alkyl having 1 to 6 carbon atoms is substituted by alkoxycarbonyl having alkoxy moiety having 1 to 6 carbon atoms, which is exemplified by methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, isobutoxycarbonylmethyl, sec-butoxycarbonylmethyl, tert-butoxycarbonylmethyl, pentyloxycarbonylmethyl, hexyloxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, propoxycarbonylethyl, isopropoxycarbonylethyl, butoxycarbonylethyl, isobutoxycarbonylethyl, sec-butoxycarbonylethyl, tert-butoxycarbonylethyl, pentyloxycarbonylethyl, hexyloxycarbonylethyl and the like.

[0074] Halogen for Q^1, Q^2 and Q^3 is as defined for R, R' and R^1. Aralkyloxy for Q^1 and Q^2 is as defined for R^3 and R^4.

[0075] Alkoxy for Q^3 is as defined for R, R' and R^1.

[0076] Alkylene for W, X and Y is linear or branched alkylene having 1 to 6 carbon atoms, which is exemplified by methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene and the like.

[0077] Alkenylene for Y is linear or branched alkenylene having 2 to 6 carbon atoms, which is exemplified by vinylene, propenylene, butenylene, pentenylene and the like.

[0078] Alkyl for Rb is as defined for R, R' and R^1.

[0079] Aralkyl for Rb is as defined for R, R' and R^1.

[0080] Aminoalkyl for Rb is as defined for L.

[0081] Mono- or dialkylaminoalkyl for Rb is as defined for L'.

[0082] The nitrogen-containing heterocycle for Rc, when it is a monocyclic ring, is exemplified by pyridine, pyrimidine, pyridazine, triazine, pyrazole, triazole and the like, and when it is a condensed ring, it is exemplified by pyrrolopyridine (e.g., 1H-pyrrolo[2,3-b]pyridine, 1H-pyrrolo[3,2-b]pyridine, 1H-pyrrolo[3,4-b]pyridine and the like), pyrazolopyridine (e.g., 1H-pyrazolo[3,4-b]pyridine, 1H-pyrazolo[4,3-b]pyridine and the like), imidazopyridine (e.g., 1H-imidazo[4,5-b]pyridine and the like), pyrrolopyrimidine (e.g., 1H-pyrrolo[2,3-d]pyrimidine, 1H-pyrrolo[3,2-d]pyrimidine, 1H-pyrrolo[3,4-d]pyrimidine and the like), pyrazolopyrimidine (e.g., 1H-pyrazolo[3,4-d]pyrimidine, pyrazolo[1,5-a]pyrimidine, 1H-pyrazolo[4,3-d]pyrimidine and the like), imidazopyrimidine (e.g., imidazo[1,2-a]pyrimidine, 1H-imidazo[4,5-d]pyrimidine and the like), pyrrolotriazine (e.g., pyrrolo[1,2-a]-1,3,5-triazine, pyrrolo[2,1-f]-1,2,4-triazine), pyrazolotriazine (e.g., pyrazolo[1,5-a]-1,3,5-triazine and the like), triazolopyridine (e.g., 1H-1,2,3-triazolo[4,5-b]pyridine and the like), triazolopyrimidine (e.g., 1,2,4-triazolo[1,5-a]pyrimidine, 1,2,4-triazolo[4,3-a]pyrimidine, 1H-1,2,3-triazolo[4,5-d]pyrimidine and the like), cinnoline, quinazoline, quinoline, pyridopyridazine (e.g., pyrido[2,3-c]pyridazine and the like), pyridopyrazine (e.g., pyrido[2,3-b]pyrazine and the like), pyridopyrimidine (e.g., pyrido[2,3-d]pyrimidine, pyrido[3,2-d]pyrimidine and the like), pyrimidopyrimidine (e.g., pyrimido[4,5-d]pyrimidine, pyrimido[5,4-d]pyrimidine and the like), pyrazinopyrimidine (e.g., pyrazino[2,3-d]pyrimidine and the like), naphthyridine (e.g., 1,8-naphthyridine and the like), tetrazolopyrimidine (e.g., tetrazolo[1,5-a]pyrimidine and the like), thienopyridine (e.g., thieno[2,3-b]pyridine and the like), thienopyrimidine (e.g., thieno[2,3-d]pyrimidine and the like), thiazolopyridine (e.g., thiazolo[4,5-b]pyridine, thiazolo[5,4-b]pyridine and the like), thiazolopyrimidine (e.g., thiazolo[4,5-d]pyrimidine, thiazolo[5,4-d]pyrimidine and the like), oxazolopyridine (e.g., oxazolo[4,5-b]pyridine, oxazolo[5,4-b]pyridine and the like), oxazolopyrimidine (e.g., oxazolo[4,5-d]pyrimidine, oxazolo[5,4-d]pyrimidine and the like), furopyridine (e.g., furo[2,3-b]pyridine, furo[3,2-b]pyridine and the like), furopyrimidine (e.g., furo[2,3-d]pyrimidine, furo[3,2-d]pyrimidine and the like), 2,3-dihydropyrrolopyridine (e.g., 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine, 2,3-dihydro-1H-pyrrolo[3,2-b]pyridine and the like), 2,3-dihydropyrrolopyrimidine (e.g., 2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidine, 2,3-dihydro-1H-pyrrolo[3,2-d]pyrimidine and the like), 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine, 5,6,7,8-tetrahydro-1,8-naphthyridine, 5,6,7,8-tetrahydroquinoline and the like. When these rings form a hydrogenated aromatic ring, the carbon atom in the ring may be carbonyl and includes, for example, 2,3-dihydro-2-oxopyrrolopyridin , 2,3-dihydro-2,3-dioxopyrrolopyridine, 7,8-dihydro-7-oxo-1,8-naphthyridine, 5,6,7,8-tetrahydro-7-oxo-1,8-naphthyridin and the like.

[0083] These rings may b substituted by a substitu nt such as halogen, alkyl, alkoxy, aralkyl, haloalkyl, nitro, amino,

alkylamino, cyano, formyl, acyl, aminoalkyl, mono- or dialkylaminoalkyl, azide, carboxy, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, alkoxyalkyl (.g., methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl and the like), optionally substituted hydrazino and the like.

[0084] As used herein, the substituent of the optionally substituted hydrazino includes alkyl, aralkyl, nitro, cyano and th lik , wherein alkyl and aralkyl are as defined for R, R' and R^1 and exemplified by methylhydrazino, ethylhydrazino, benzylhydrazino and the like.

[0085] The compound of the formula (I) is exemplified by the following compounds.

(1) 4-(2-pyridylcarbamoyl)piperidine
(2) 1-benzyloxycarbonyl-4-(4-pyridylcarbamoyl)piperidine
(3) 1-benzoyl-4-(4-pyridylcarbamoyl)piperidine
(4) 1-propyl-4-(4-pyridylcarbamoyl)piperidine
(5) 1-[3-(2-(2-thienylmethyl)phenoxy)-2-hydroxypropyl]-4-(4-pyridylcarbamoyl)piperidine
(6) 4-(4-pyridylcarbamoyl)piperidine
(7) 1-benzyl-4-(4-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine
(8) 3-(4-pyridylcarbamoyl)piperidine .
(9) 1-benzyl-3-(4-pyridylcarbamoyl)piperidine
(10) 1-(2-(4-benzyloxyphenoxy)ethyl)-4-(N-(2-pyridyl)-N-benzylcarbamoyl)piperidine
(11) 1-formyl-4-(4-pyridylcarbamoyl)piperidine
(12) 4-(3-pyridylcarbamoyl)piperidine
(13) 1-isopropyl-4-(4-pyridylcarbamoyl)piperidine
(14) 1-methyl-4-(4-pyridylcarbamoyl)piperidine
(15) 1-hexyl-4-(4-pyridylcarbamoyl)piperidine
(16) 1-benzyl-4-(4-pyridylcarbamoyl)piperidine
(17) 1-(2-phenylethyl)-4-(4-pyridylcarbamoyl)piperidine
(18) 1- (2- (4-methoxyphenyl)ethyl)-4- (4-pyridylcarbamoyl)-piperidine
(19) 1-(2-(4-methoxyphenyl)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(20) 1-(2-(4-chlorophenyl)ethyl)-4-(4-pyridylcarbamoyl)-piperidine
(21) 1-diphenylmethyl-4-(2-pyridylcarbamoyl)piperidine
(22) 1-[2-(4-(5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)phenyl)ethyl]-4-(2-pyridylcarbamoyl)piperidine
(23) 1-(4-(4,5-dihydro-2-furyl)phenyl)-4-(4-pyridylcarbamoyl) piperidine
(24) 1-(2-nitrophenyl)-4-(4-pyridylcarbamoyl)piperidine
(25) 1-(2-aminophenyl)-4-(4-pyridylcarbamoyl)piperidine
(26) 1-nicotinoyl-4-(4-pyridylcarbamoyl)piperidine
(27) 1-isonicotinoyl-4-(4-pyridylcarbamoyl)piperidine
(28) 1-(3,4,5-trimethoxybenzoyl)-4-(4-pyridylcarbamoyl)-piperidine
(29) 1-acetyl-4-(4-pyridylcarbamoyl)piperidine
(30) 1-(3-(4-fluorobenzoyl)propyl)-4-(4-pyridylcarbamoyl)-piperidine
(31) 1-(3-(4-fluorobenzoyl)propyl)-4-(2-pyridylcarbamoyl)-piperidine
(32) 1-(1-(4-hydroxybenzoyl)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(33) 1-(1-(4-benzyloxybenzoyl)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(34) 1-(2-(4-hydroxyphenoxy)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(35) 1-(4-(4-fluorophenyl)-4-hydroxybutyl)-4-(4-pyridylcarbamoyl)piperidine
(36) 1-(1-methyl-2-(4-hydroxyphenyl)-2-hydroxyethyl)-4-(2-pyridylcarbamoyl)piperidine
(37) 1-cinnamyl-4-(2-pyridylcarbamoyl)piperidine
(38) 1-(2-hydroxy-3-phenoxypropyl)-4-(4-pyridylcarbamoyl)-piperidine
(39) 1-(2-hydroxy-3-phenoxypropyl)-4-(3-pyridylcarbamoyl)-piperidine
(40) 1-(2-hydroxy-3-phenoxypropyl)-4-(2-pyridylcarbamoyl)-piperidine
(41) 1-(2-phenylethyl)-4-[N-(2-pyridyl)-N-(2-(N,N-dimethylamino)ethyl)carbamoyl]piperidine
(42) 1-benzyloxycarbonyl-4-(2-pyridylcarbamoyl)piperidine
(43) 1-(3-chlorophenyl)carbamoyl-4-(4-pyridylcarbamoyl)-piperidine
(44) 4-[N-(2-pyridyl)-N-(2-(N,N-dimethylamino)ethyl)-carbamoyl]piperidine
(45) 1-methyl-4-(4-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine
(46) 1-nicotinoyl-3-(4-pyridylcarbamoyl)piperidine
(47) 1-[2-(4-fluorobenzoyl)ethyl]-4-(4-pyridylcarbamoyl)-piperidine
(48) 1-(6-chloro-2-methylimidazo[1,2-a]pyridine-3-carbonyl)-4-(4-pyridylcarbamoyl)piperidine
(49) 1-(4-nitrobenzyl)-4-(4-pyridylcarbamoyl)piperidine
(50) 1-hexyl-4-(4-pyridylcarbamoyl)piperidine

(51) 1-b nzyloxycarbonyl-4-(2-chloro-4-pyridylcarbamoyl)-pip ridine
(52) 4-(2-chloro-4-pyridylcarbamoyl)pip ridine
(53) 1-(2-chloronicotinoyl)-4-(4-pyridylcarbamoyl)piperidine
(54) 3-(2-chloro-4-pyridylcarbamoyl)pip ridine
(55) 1-(4-phthalimidobutyl)-4-(4-pyridylcarbamoyl)piperidine
(56) 1-(3,5-di-tert-butyl-4-hydroxycinnamoyl)-4-(4-pyridylcarbamoyl) piperidine
(57) 1-carbamoylmethyl-4-(4-pyridylcarbamoyl)piperidine
(58) 1-benzyloxycarbonyl-4-(5-nitro-2-pyridylcarbamoyl)-piperidine
(59) 4-(5-nitro-2-pyridylcarbamoyl)piperidine
(60) trans-4-benzyloxycarboxamidomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(61) trans-4-aminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(62) trans-4-formamidomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(63) trans-4-dimethylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(64) N-benzylidene-trans-(4-pyridylcarbamoyl)-cyclohexylmethylamine
(65) trans-4-benzylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(66) trans-4-isopropylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(67) trans-4-nicotinoylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(68) trans-4-cyclohexylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(69) trans-4-benzyloxycarboxamide-1-(4-pyridylcarbamoyl)-cyclohexane
(70) trans-4-amino-1-(4-pyridylcarbamoyl)cyclohexane
(71) trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(72) trans-4-aminomethyl-cis-2-methyl-1-(4-pyridylcarbamoyl)-cyclohexane
(73) (+)-trans-4-(1-benzyloxycarboxamidopropyl)-1-cyclohexanecarboxylic acid
(74) (+)-trans-4-(1-benzyloxycarboxamidopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
(75) (-)-trans-4-(1-benzyloxycarboxamidopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
(76) (+)-trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(77) (-)-trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(78) (-)-trans-4-(1-benzyloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(79) (+)-trans-4-(1-benzyloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(80) (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(81) (-)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(82) trans-4-(4-chlorobenzoyl)aminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(83) trans-4-aminomethyl-1-(2-pyridylcarbamoyl)cyclohexane
(84) trans-4-benzyloxycarboxamidomethyl-1-(2-pyridylcarbamoyl)cyclohexane
(85) trans-4-methylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(86) trans-4-(N-benzyl-N-methylamino)methyl-1-(4-pyridylcarbamoyl)cyclohexane
(87) trans-4-aminomethyl-1-(3-pyridylcarbamoyl)cyclohexane
(88) trans-4-aminomethyl-1-[(3-hydroxy-2-pyridyl)carbamoyl]-cyclohexane
(89) trans-4-benzyloxycarboxamidomethyl-1-(3-pyridylcarbamoyl)cyclohexane
(90) trans-4-benzyloxycarboxamidomethyl-1-[(3-benzyloxy-2-pyridyl)carbamoyl]cyclohexane
(91) trans-4-phthalimidomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(92) trans-4-benzyloxycarboxamidomethyl-1-(3-methyl-4-pyridylcarbamoyl)cyclohexane
(93) trans-4-aminomethyl-1-(3-methyl-4-pyridylcarbamoyl)-cyclohexane
(94) 4-(trans-4-benzyloxycarboxamidomethylcyclohexylcarbonyl)amino-2,6-dimethylpyridine-N-oxide
(95) 4-(trans-4-aminomethylcyclohexylcarbonyl)amino-2,6-dimethylpyridine-N-oxide
(96) trans-4-aminomethyl-1-(2-methyl-4-pyridylcarbamoyl)-cyclohexane
(97) trans-4-(1-benzyloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(98) trans-4-(1-amino-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(99) trans-4-(2-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(100) trans-4-(2-amino-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(101) trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(102) trans-4-aminomethyl-trans-1-methyl-1-(4-pyridylcarbamoyl)cyclohexane
(103) trans-4-benzylaminomethyl-cis-2-methyl-1-(4-pyridylcarbamoyl)cyclohexane
(104) trans-4-(1-benzyloxycarboxamide-1-methylethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(105) trans-4-benzyloxycarboxamidomethyl-1-(N-methyl-4-pyridylcarbamoyl)cyclohexane
(106) trans-4-(1-acetamide-1-methylethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(107) trans-N-(6-amino-4-pyrimidyl)-4-aminomethylcycloh xanecarboxamide
(108) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminom thylcyclohexanecarboxamide

(109) (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(110) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexan carboxamid
(111) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(112) (+)-trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(113) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cycloh xanecarboxamide
(114) (+)-trans-N-(2-amino-4-pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide
(115) trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
(116) (+)-trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(117) trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(118) trans-N-(4-pyrimidinyl)-4-aminomethylcyclohexanecarboxamide
(119) trans-N-(3-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(120) trans-N-(7H-imidazo[4,5-d]pyrimidin-6-yl)-4-aminomethylcyclohexanecarboxamide
(121) trans-N-(3H-1,2,3-triazolo[4,5-d]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
(122) trans-N-(1-benzyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(123) trans-N-(1H-5-pyrazolyl)-4-aminomethylcyclohexanecarboxamide
(124) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(125) trans-N-(4-pyridazinyl)-4-aminomethylcyclohexanecarboxamide
(126) trans-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
(127) trans-N-(2-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(128) trans-N-(thieno[2,3-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
(129) trans-N-(5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
(130) trans-N-(3-cyano-5-methylpyrazolo[1,5-a]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
(131) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-1-methylethyl) cyclohexanecarboxamide
(132) trans-N-(2-(1-pyrrolidinyl)-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(133) trans-N-(2,6-diamino-4-pyrimidyl)-4-aminomethylcyclohexanecarboxamide
(134) (+)-trans-N-(7-methyl-1,8-naphthyridin-4-yl)-4-(1-aminoethyl) cyclohexanecarboxamide
(135) trans-N-(1-benzyloxymethylpyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(136) (+)-trans-N-(1-methylpyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(137) trans-N-benzyl-N-(2-benzylamino-4-pyridyl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(138) trans-N-(2-azide-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(139) trans-N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(140) trans-N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(141-1) trans-N-(2-carboxy-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(141-2) (R)-(+)-trans-N-(3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(142) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
(143) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
(144) trans-N-(4-pyridyl)-4-guanidinomethylcyclohexanecarboxamide
(145) trans-N-(1-methylpyrrolo[2,3-b]pyridin-4-yl)-4-(guanidinomethyl)cyclohexanecarboxamide
(146) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(2-imidazolin-2-yl)aminomethylcyclohexanecarboxamide
(147) trans-N-(1-benzyloxymethylpyrrolo[2,3-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
(148) trans-N-(2-amino-4-pyridyl)-4-guanidinomethylcyclohexanecarboxamide
(149) trans-N-(1-benzyloxymethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(2-imidazolin-2-yl)aminomethylcyclohexanecarboxamide
(150) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-benzylguanidinomethyl)cyclohexanecarboxamide
(151) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-phenylguanidinomethyl)cyclohexanecarboxamide
(152) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-propylguanidinomethyl)cyclohexanecarboxamide
(153) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-octylguanidinomethyl)cyclohexanecarboxamide
(154) trans-N-(1-benzyloxymethylpyrrolo[2,3-b]pyridin-4-yl)-4-(2-benzyl-3-ethylguanidinomethyl)cyclohexanecarboxamide
(155) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(imidazol-2-yl)aminomethylcyclohexanecarboxamide
(156) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(thiazol-2-yl)aminomethylcyclohexanecarboxamide
(157) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide
(158) N-(4-pyridyl)-4-(1-amino-1-methylethyl)benzamide
(159) N-(4-pyridyl)-4-aminomethyl-2-benzyloxybenzamide
(160) N-(4-pyridyl)-4-aminomethyl-2-ethoxybenzamide
(161) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-nitrobenzamide
(162) (R)-(-)-N-(4-pyridyl)-3-amino-4-(1-aminoethyl)benzamide
(163) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-3-chlorobenzamide

(164) N-(4-pyridyl)-3-aminomethylbenzamide
(165) (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)b nzamid
(166) (R)-(+)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino thyl)benzamide
(167) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethylb nzamide
(168) N-(4-pyridyl)-4-guanidinomethylbenzamide
(169) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-3-fluorobenzamide
(170) N-(4-pyridyl)-4-aminomethylbenzamide
(171) N-(4-pyridyl)-4-aminomethyl-2-hydroxybenzamide
(172) N-(4-pyridyl)-4-(2-aminoethyl)benzamide
(173) N-(4-pyridyl)-4-aminomethyl-3-nitrobenzamide
(174) N-(4-pyridyl)-3-amino-4-aminomethylbenzamide
(175) (S)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide
(176) (S)-(-)-N-(4-pyridyl)-2-(1-aminoethyl)benzamide
(177) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-2-chlorobenzamide
(178) (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-(3-propylguanidino)ethyl)benzamide
(179) (R)-(-)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-3-azidebenzamide
(180) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-2-nitrobenzamide
(181) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-ethoxybenzamide
(182) (R)-(+)-N-(3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
(183) (R)-(+)-N-(3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-3-azidebenzamide
(184) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-hydroxybenzamide
(185) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethyl-3-nitrobenzamide
(186) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-guanidinoethyl)-3-nitrobenzamide
(187) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)-2-nitrobenzamide
(188) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinobenzamide
(189) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)-3-nitrobenzamide
(190) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-guanidinoethyl)benzamide
(191) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-2-hydroxyethyl)benzamide
(192) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethyl-3-nitrobenzamide
(193) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-piperidinecarboxamide
(194) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-piperidinecarboxamide
(195) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-aminoacetyl-4-piperidinecarboxamide
(196) N-(1-methoxymethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-4-piperidinecarboxamide
(197) N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-piperidinecarboxamide
(198) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(2-phenylethyl)-4-piperidinecarboxamide
(199) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-amidino-4-piperidinecarboxamide
(200) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(3-phenylpropyl)-4-piperidinecarboxamide
(201) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-benzyl-4-piperidinecarboxamide
(202) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-(2-phenylethyl)-4-piperidinecarboxamide
(203) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-(3-phenylpropyl)-4-piperidinecarboxamide
(204) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)benzamide

[0086] Preferred are compounds (80) , (109) , (110), (112), (115), (142) , (143), (144), (145) , (153), (157) , (163), (165) , (166) and (179). More preferred are compound (165) and hydrochloride thereof, and particularly preferred is monohydrochloride of compound (165).

[0087] The compound having a Rho kinase inhibitory activity may be a pharmaceutically acceptable acid addition salt, wherein the acid is exemplified by inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, and organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, tartaric acid, salicylic acid and the like. A compound having a carboxyl group can be converted to a salt with a metal such as sodium, potassium, calcium, magnesium, aluminum and the like, a salt with an amino acid such as lysine and the like. Further, monohydrate, dihydrate, 1/2 hydrate, 1/3 hydrate, 1/4 hydrate, 2/3 hydrate, 3/2 hydrate, 6/5 hydrate and the like are encompassed in the present invention.

[0088] The compound to be used as a compound having Rho kinase inhibitory activity of the present invention may be provided as a prodrug. As used herein, the prodrug is a compound that can be converted to the aforementioned compound having Rho kinase inhibitory activity in living organisms, and, for example, a compound wherein a moiety in the molecule of th compound of the formula (I), such as carboxyl group (COOH), hydroxyl group (OH), amino group (NH_2, including amid), mercapto group (SH) and th like, is modified (Developm nt of Pharmaceutical Product, vol. 7 (molecul design) Hirokawa Shot n).

[0089] The compound of the formula (I) can be synthesized by a method described in, for exampl , JP-A-62-89679, JP-A-3-218356, JP-A-5-194401, JP-A-6-41080, WO95/28387, WO98/06433 and th like. The thiochroman compounds can be synthesized by a method described in WO01/68607 and th like, th isoquinolinesulfonamide derivative can b synthesized by a method described in US4678783 and the like, and vinylbenzen derivativ can be synthesized by a method described in JP-A-2000-44513 and the like.

[0090] When the above-mentioned compound having a Rho kinase inhibitory activity has an optical isomer, its racemate or cis-trans isomers, all of them can be used in the present invention. These isomers can be isolated by a conventional method or can be produced using starting materials of the isomers.

[0091] The acid addition salt, hydrate and prodrug can be produced by a conventional method.

[0092] When a compound having Rho kinase inhibitory activity is used as a pharmaceutical agent, particularly, as a visual function disorder improving agent or an agent for promoting extension of axon of a retinal ganglion cell or an agent for promoting regeneration of an optic nerve cell of the present invention, it is prepared as a general pharmaceutical preparation.

[0093] For example, the compound having a Rho kinase inhibitory activity is mixed with a carrier acceptable for formulation of a preparation (e.g., excipient, binder, disintegrator, corrective, corrigent, emulsifier, diluent, solubilizer and the like) to give a pharmaceutical composition, which is formulated into a preparation in the form suitable for oral or parenteral preparation, such as tablet, pill, powder, granule, capsule, troche, syrup, liquid, emulsion, suspension, injection (e.g., liquid, suspension and the like), suppository, inhalant, percutaneous absorber, eye drop, eye ointment, preparation to be embedded in the eye and the like.

[0094] When preparing a solid preparation, additives such as sucrose, lactose, cellulose sugar, D-mannitol, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectines, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, calcium phosphate, sorbitol, glycine, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, glycerol, polyethylene glycol, sodium hydrogencarbonate, magnesium stearate, talc and the like are used. Tablets can be applied with a typical coating, where necessary, to give sugar coated tablets, enteric tablets, film-coated tablets, two-layer tablets and multi-layer tablets.

[0095] When preparing a semi-solid preparation, animal and plant fats and oils (e.g., olive oil, corn oil, castor oil and the like), mineral fats and oils (e.g., petrolatum, white petrolatum, solid paraffin and the like), wax (e.g., jojoba oil, carnauba wax, bee wax and the like), partly or entirely synthesized glycerol fatty acid esters (e.g., lauric acid, myristic acid, palmitic acid and the like), and the like are used. Examples of commercially available products of these include Witepsol (manufactured by Dynamitnovel Ltd.), Farmazol (manufactured by NOF Corporation) and the like.

[0096] When preparing a liquid preparation, an additive, such as sodium chloride, glucose, sorbitol, glycerol, olive oil, propylene glycol, ethyl alcohol and the like, is used. When preparing an injection, a sterile aqueous solution such as physiological saline, isotonic solution, oily solution (e.g., sesame oil and soybean oil) and the like are used. Where necessary, a suitable suspending agent such as sodium carboxymethylcellulose, nonionic surfactant, solubilizer (e.g., benzyl benzoate and benzyl alcohol), and the like can be concurrently used. Moreover, when an eye drop is prepared, an aqueous liquid or solution is used, which is particularly a sterile injectable aqueous solution. The eye drop can appropriately contain various additives such as buffer (borate buffer, acetate buffer, carbonate buffer, sodium dihydrogen phosphate, disodium hydrogen phosphate and the like are preferable for reducing irritation), isotonicity agent (sodium chloride, conc. grycerol, mannitol, glucose and the like), solubilizer, preservative (chlorobutanol, benzyl alcohol, sodium dehydroacetate, benzalkonium chloride, boric acid and the like), thickener (hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol) and the like, chelating agent (sodium edetate, sodium citrate and the like), pH adjusting agent (generally, pH is preferably adjusted to about 6 - 8 by hydrochloric acid, sodium hydroxide, phosphoric acid or acetic acid) and aromatic.

[0097] When a preparation to be embedded in the eye is to be produced, a biodegradable polymer, such as polylactic acid, polyglycolic acid, lactic acid glycolic acid copolymer, hydroxypropyl cellulose and the like, can be used.

[0098] The dose of the active ingredient of these preparations, is 0.1 - 100 wt%, suitably 1 - 50 wt%, of the preparation. While the dose varies depending on the symptom, body weight, age and the like of patients, it is generally about 1 - 500 mg a day for an adult, which is administered once to several times a day.

[0099] For topical administration into the eye drop, an eye drop containing a compound having Rho kinase inhibitory activity in a proportion of about 0.0001 - about 10 w/v%, preferably about 0.001 - about 1 w/v%, is preferably administered by several drops, preferably 1-3 drops, per administration several times, preferably 1-6 times, per one day. For administration as a preparation to be embedded in the eye, a preparation to be embedded in the eye, which contains a compound having Rho kinase inhibitory activity in a proportion of about 0.0001 - about 1 mg, preferably about 0.001 - about 0.5 mg, is prepared into a short rod, a needle, a film, a tablet, a microcapsule or fine sphere and the like according to the method described in, for example, JP-A-1-216917, JP-A-3-170418 (corresponding to EP430539 and US5164188) and JP-A-5-17370 (corresponding to EP488401 and US5501856) and the like and, for example, preferably buried in the vitreous body.

Examples

[0100] The present invention is explained in detail by referring to formulation examples and pharmacological action. The present invention is not limited in any way by the examples.

[0101] In the following Preparative Formulation Examples and Experimental Examples, a compound having Rho kinase inhibitory activity, such as (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide dihydrochloride 3/2 hydrate (hereinafter to be also referred to as compound 1), (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride (hereinafter to be also referred to as compound 2), 4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid (hereinafter to be also referred to as compound 3), ethacrynic acid (hereinafter to be also referred to as compound 4) or fasudil hydrochloride (hereinafter to be also referred to as compound 5), was used.

Formulation Example 1: Tablet	
Compound of the present invention	
(compound 1)	10.0 mg
Lactose	50.0 mg
Cornstarch	20.0 mg
Crystalline cellulose	29.7 mg
Polyvinylpyrrolidone K30	5.0 mg
Talc	5.0 mg
Magnesium stearate	0.3 mg
	120.0 mg

[0102] The compound of the present invention (compound 1), lactose, cornstarch and crystalline cellulose were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve, and talc and magnesium stearate were added. Using a ϕ7 mm punch, tablets weighing 120 mg per tablet were prepared.

Formulation Example 2 : Capsules	
Compound of the present invention	
(compound 1)	10.0 mg
Lactose	70.0 mg
Cornstarch	35.0 mg
Polyvinylpyrrolidone K30	2.0 mg
Talc	2.7 mg
Magnesium stearate	0.3 mg
	120.0 mg

[0103] The compound of the present invention (compound 1), lactose and cornstarch were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve and talc and magnesium stearate were added. The mixture was filled in a hard capsule (No. 4) to give a capsule weighing 120 mg.

Preparative Formulation Example 3: Eye drop	
Compound of the present invention	
(compound 2)	0.05 g
sodium dihydrogen phosphate	0.1 g
sodium chloride	0.85 g
benzalkonium chloride	0.005 g
sterilized purified water	total amount 100 mL
pH	7.0

[0104] Th compound of the present invention (compound 2), sodium dihydrogen phosphat , sodium chloride and benzalkonium chloride wer dissolved in sterilized purified water (ca. 80 mL). Th pH was adjusted to 7.0 with hydrochloric acid and sodium hydroxide and sterilized purified water was added to th total amount of 100 mL to give an eye drop.

[0105] Using compound 3, compound 4 or compound 5 instead of compound 2, an ye drop is prepared in the sam manner.

Preparative Formulation Example 4: Preparation to be embedded in the eye	
compound of the present invention (compound 2)	0.1 g
lactic acid-glycolic acid copolymer (lactic acid:glycolic acid=75:25, molecular weight 5000)	1.0 g

[0106] The compound of the present invention (compound 2) and lactic acid-glycolic acid copolymer are mechanically mixed and melted at about 80°C to give a homogeneous mixture. After cooling to allow solidification, the mixture is pulverized in a mortar. The pulverized product (3 mg) was filled in a Teflon tube having an inner diameter of 0.8 mm. The both ends of the Teflon tube filled with the pulverized product was pressed while heating to about 80°C to give a short rod preparation to be embedded in the eye having a diameter of 0.8 mm and a length of 3 mm.

[0107] Using compound 3, compound 4 or compound 5 instead of compound 2, a preparation to be embedded in the eye is prepared in the same manner.

Preparative Formulation Example 5: Tablet	
compound of the present invention	
(compound 2)	10 mg
lactose	80 mg
starch	17 mg
magnesium stearate	3 mg
crystalline cellulose	10 mg

[0108] Using the above components as materials for one tablet, a tablet is formed by a conventional method. This tablet may be coated as necessary with a sugar coating, a film (e.g., ethylcellulose etc.) to be generally used and the like.

[0109] Using compound 3, compound 4 or compound 5 instead of compound 2, a tablet is prepared in the same manner.

Preparative Formulation Example 6: Capsule	
compound of the present invention	
(compound 2)	10 mg
mannitol	75 mg
starch	17 mg
magnesium stearate	3 mg

[0110] Using the above components as materials for one capsule, granule is produced by a conventional method and filled in a hard capsule. The granule to be filled may be coated as necessary with a film (e.g., ethylcellulose etc.) to be generally used and the like.

[0111] Using compound 3, compound 4 or compound 5 instead of compound 2, a capsule is prepared in the same manner.

Preparative Formulation Example 7: Injection	
compound of the present invention	
(compound 2)	150 mg
sodium chloride	900 mg
1N sodium hydroxide	suitable amount

(continued)

Preparative Formulati n Example 7: Injection	
compound of th pres nt invention	
distilled water for injection	total amount 100 mL

[0112] The above components are admixed according to a conventional method to give an injection, from which 0.1 mL is injected into the vitreous body.

[0113] Using compound 3, compound 4 or compound 5 instead of compound 2, an injection is prepared in the same manner.

[0114] In the following, the pharmacological action of the pharmaceutical agent of the present invention is explained by Examples.

Example 1 (in vitro experiment)

(1) Method

[0115] Retinal ganglion cells were isolated from an eye ball of a Wistar rat, and cultured in a 48 well plate coated with polylysin (50 μg/mL, Sigma) and merosin (2 μg/mL, GIBCO) at 37°C under the environment of 5% CO_2, 95% air. The number of the cells was about 5000 cells/well. The culture solutions were a culture solution (fetal calf serum-free culture solution) of Neurobasal Medium (GIBCO) supplemented with 50 ng/mL BDNF (human brain-derived neurotrophic factor, Sigma), 50 ng/mL CNTF (rat cilliary neurotrophic factor, Sigma), 5 μM forskolin (Sigma), 1 mM glutamine (Wako) and B27 Supplement (GIBCO; 1 mL/50 mL culture solution), and a culture solution (FCS supplemented culture solution) of the aforementioned fetal calf serum-free culture solution supplemented with 10% fetal calf serum (hereinafter to be also referred to as FCS). After culture for 24 hrs in each culture solution, the group cultured in the FCS supplemented culture solution was divided into 2 groups, and one of them was used as a compound 1 addition group with the addition of 10 μM of compound 1, and the other was used as a compound 1 non-addition group. Similarly, the group cultured in the FCS-free culture solution was divided into a compound 1 addition group and a compound 1 non-addition group. After further culture for 24 hrs, the level of extension of nerve axon of a retinal ganglion cell was observed under an inverted light microscope.

(2) Results

[0116] The results are shown in Fig. 1. In Fig. 1, A shows a retinal ganglion cell cultured for 48 hrs in an FCS-supplemented culture solution, B shows a retinal ganglion cell which was cultured in an FCS-supplemented culture solution for 24 hrs, and after addition of 10 μM compound 1, further cultured for 24 hrs, C shows a retinal ganglion cell cultured in an FCS-free culture solution for 48 hrs, and D shows a retinal ganglion cell cultured in an FCS-free culture solution for 24 hrs, and after addition of 10 μM compound 1, further cultured for 24 hrs.

[0117] The retinal ganglion cell cultured in an FCS-supplemented culture solution for 48 hrs hardly showed formation of neurite (A). When the retinal ganglion cell was cultured for 24 hrs in an FCS-supplemented culture solution, added with 10 μM compound 1 and further cultured for 24 hrs, the retinal ganglion cell formed a neurite at a high speed (extension of nerve axon), and clearly showed a retinal ganglion cell nerve axon extending action, as compared to compound 1 non-addition group (B).

[0118] In a retinal ganglion cell cultured in an FCS-free culture solution from the start of the culture, too, the extension of nerve axon was observed (C). In contrast, when compound 1 was added to an FCS-free culture solution, the extension of nerve axon became remarkable and an action of the compound 1 to promote extension of the nerve axon was confirmed (D).

[0119] From the above, it has been found that the compound 1 has an action of extension of nerve axon of a retinal ganglion cell and an action of promotion of extension of axon.

[0120] While this Experimental Example discloses only the experimental results using Wister rats, SD rats were also subjected to a similar experiment. As a result, similar axonal extension action and axonal extension promoting action of compound 1 were observed in the retinal ganglion cell.

Exampl 2 (in vivo experiment)

(1) Method

[0121] Th optic nerve of SD rats w ighing 220-280 g was cut under pentobarbital sodium (0.4 mg/kg, i.p.) anesth - sia. Separately, the sciatic nerve of the optic nerve-severed rat was taken out in about 3-4 cm and autografted at an end of the optic nerve, which had been cut earlier. The compound 1 dissolved to 120 μmol/L was injected into the vitreous body by 5 μL immediately before cutting the optic nerve, and gelatin pieces (3 mm x 3 mm; Spongel, Yamanouchi Pharm.) immersed in a 10 μmol/L solution of compound 1 were embedded around the autograft (compound 1 treatment group). For the non-treatment group, physiological saline was used instead of compound 1 for both the injection into the vitreous body and preparation of the gelatin pieces. During the grafting, attention was.paid to avoid damage to the ophthalmic artery, and after grafting, the retinal vascular network was confirmed with a funduscope before breeding under a temperature 23°C±2, humidity 55±10% environment. The rats were allowed to have a free access to a feed and water. After 6 weeks from the grafting operation, the graft was transversely cut under pentobarbital sodium (0.4 mg/kg, i.p.) anesthesia, and gelatin pieces immersed in 10% GB (p-amidinophenyl p-(6-amidino-2-indolyl) phenyl ether, Sigma, St. Louis, MO) were embedded in the cut area of the graft, thereby to retrogradely label retinal ganglion cells. After 48 hrs, the eye ball of the rat was enucleated and a retinal extension sample was prepared according to a conventional method. The images of the retinal extension samples observed under a microscope were directly imported into computer images from the fluorescence microscope and the retrogradedly labeled retinal ganglion cells were counted using an image analyzing soft (MacSCOP, MITANI CO.). The obtained number of the retrogradedly labeled retinal ganglion cells was taken as a regenerated optic nerve cells. Meanwhile, the optic nerve of the rat free of grafting was cut, gelatin pieces immersed in 10% GB were embedded similarly, and 48 hrs later, the number of the labeled retinal ganglion cells of the retinal extension sample was taken as the number of optic nerve cells of the control.

[0122] The ratios (%) of the regenerated cell counts of the non-treatment group and compound 1 treatment group, relative to the optic nerve cell counts of the control, were calculated.

(2) Results

[0123] The results are shown in Fig. 2. The regenerated optic nerve cell count of the non-treatment group was about 5% of that of the control group. In contrast, the regenerated optic nerve cell count of the compound 1 treatment group was about 12% of the control group and about 2.4 times that of the non-treatment group.

[0124] From the above, it has been found that compound 1 has an optic nerve cell regeneration promoting action.

Example 3 (in vitro experiment)

(1) Method

[0125] Retinal ganglion cells were isolated from an eye ball of a Wistar rat and cultured in a 48 well plate coated with polylysine (50 μg/mL, Sigma) and merosin (2 μg/mL, GIBGO) at 37°C under the environment of 5% CO_2, 95% air. The number of cells was about 5000 cells/well. The culture solution was a culture solution (FCS-free culture solution) of Neurobasal Medium (GIBCO) supplemented with 50 ng/mL BDNF (human brain-derived neurotrophic factor, Sigma), 50 ng/mL CNTF (rat cilliary neurotrophic factor, Sigma), 5 μM forskolin (Sigma), 1 mM glutamine (Wako) and B27 Supplement (GIBCO; 1 mL/50 mL culture solution). After culture for 24 hrs in a culture solution of the aforementioned FCS-free culture solution supplemented with 10% FCS (FCS-supplemented culture solution containing Rho activator) and an FCS-free culture solution, the group cultured in the FCS-free culture solution was divided into 2 groups, and one of them was used as a compound 2 addition group with the addition of 10 μM of compound 2, and the other was used as a compound 2 non-addition group. After further culture for 24 hrs, the level of extension of nerve axon of a retinal ganglion cell was observed under an inverted light microscope. In addition, 1 μM lysophosphatidic acid (LPA), which is a Rho activator, was added to an FCS-free group and axon retraction due to Rho activation was also examined.

(2) Results

[0126] The results are shown in Fig. 3. In Fig. 3, A shows a retinal ganglion cell cultured for 48 hrs in an FCS-supplemented culture solution, B shows a retinal ganglion cell cultured for 48 hrs in an FCS-free culture solution for 48 hrs, C shows a retinal ganglion cell cultured in an FCS-free culture solution for 24 hrs, and after addition of 10 μM compound 2, further cultured for 24 hrs, and D shows a retinal ganglion cell cultured in an FCS-free culture solution for 44 hrs, and after addition of 1 μM LPA, further cultured for 4 hrs.

[0127] Th retinal ganglion cell cultured for 48 hrs in an FCS-supplemented culture solution, containing a Rho acti-

vator in the early stages of culture, hardly showed formation of neurite (A). A retinal ganglion cell cultured in an FCS-free culture solution from th start of th culture showed a short xt nsion of nerve axon (B). When cultured for 24 hrs in an FCS-free culture solution, added with 10 μM compound 2 and furth r cultured for 24 hrs, th retinal ganglion cell xtended the nerve axon at a high speed, and clearly showed an action of extending the n rve axon of the retinal ganglion cell (C). In th addition group wh r an FCS-free cultur solution suppl m nted with 1 μM of LPA was used, an axon retraction effect due to the activation of Rho was observed (D).

[0128] From the above, it has been found that compound 2 has a nerve axon extending action and a promoting action on extension of nerve axon of a retinal ganglion cell. These actions were suppressed by activation of Rho.

Example 4 (in vivo experiment)

(1) Method

[0129] The optic nerve of SD rats weighing 220-280 g was cut under pentobarbital sodium (0.4 mg/kg, i.p.) anesthesia. Separately, the sciatic nerve of the optic nerve-severed rat was taken out in about 3-4 cm and autografted at an end of the optic nerve, which had been cut earlier. The compound 2 dissolved to 120 μM was injected into the vitreous body by 5 μL immediately before cutting the optic nerve, and gelatin pieces (3 mm × 3 mm; Spongel, Yamanouchi Pharm.) immersed in a 10 μM solution of compound 2 were embedded around the autograft (compound 2 treatment group - 1). For compound 2 treatment group - 2, the compound 2 dissolved to 1.2 mM was injected into the vitreous body by 5 μL and 100 μM of compound 2 was used around the graft. In the control group, physiological saline was used instead of compound 2. During the grafting, attention was paid to avoid damage to the ophthalmic artery, and after grafting, the retinal vascular network was confirmed with a funduscope before breeding under a temperature 23°C±2, humidity 55±10% environment. The rats were allowed to have a free access to a feed and water. After 6 weeks from the grafting operation, the graft was transversely cut under pentobarbital sodium (0.4 mg/kg, I.p.) anesthesia, and 4-Di-10ASP [4-(4-didecylaminostyryl)-N-methylpropidium iodide, Sigma, St. Louis, MO] crystal (ca. 2 mg) was embedded in the cut area of the graft, thereby to retrogradely label retinal ganglion cells. After 3 days, the eye ball of the rat was enucleated and a retinal extension sample was prepared according to a conventional method. The images of the retinal extension samples observed under a microscope were directly imported into computer images from the fluorescence microscope and the retrogradely labeled retinal ganglion cells were counted using an image analyzing soft (MacSCOP, MITANI CO.)(Fig. 4). The obtained number of the retrogradely labeled retinal ganglion cells was taken as indicating the regenerated optic nerve cells. Meanwhile, the optic nerve of the rat free of grafting was cut, 4-Di-10ASP crystal (ca. 2 mg) was embedded similarly, and the number of the labeled retinal ganglion cells of the retinal extension sample was taken as the number of optic nerve cells of the normal group.

[0130] The ratios (%) of the regenerated optic nerve cell counts of the control group, compound 2 treatment group - 1 and compound 2 treatment group - 2, relative to the optical nerve cell counts of the control, were calculated.

(2) Results

[0131] The regenerated optic nerve cell count of the control group was about 7% of the normal group. In contrast, the regenerated optic nerve cell count of the compound 2 treatment group - 1 was about 16% of the normal group, and the regenerated optic nerve cell count of the compound 2 treatment group - 2 was about 28% of the normal group. They were about 2.3 times and about 4 times that of the control group (Fig. 5).

[0132] From the above, it has been found that compound 2 promotes regeneration of the optic nerve cells.

Example 5 (in vitro experiment)

(1) Method

[0133] In the same manner as in Examples 1 and 3, retinal ganglion cells isolated from the eye ball of 6 to 8-day-old Wistar rats (male-female mixture, SLC) were cultured (cell count: ca. 2000 cells/well). The test compounds (compounds 3-5) were added to the culture solution to the final concentration of 10 μM and respectively used as compound 3 addition group, compound 4 addition group and compound 5 addition group. The control was a test compound non-addition group. The compound 3 (4-[2-(2,3,4,5,6-pentafluorophenyl)acryloyl]cinnamic acid) was synthesized according to the description of Example 8 of JP-A-2000-44513 and used. As compound 4 (ethacrynic acid), one made by Sigma was used and as compound 5 (fasudil hydrochloride), a commercially-available fasudil hydrochloride hydrate injection: "Eril® Injecti n 30 mg" (produced and sold by Asahi Kasei Corporation) was used.

[0134] Using LIVE/DEAD® Viability/Cytotoxicity Kit (L-3224)(Molecular probes) and utilizing the fluoresc nc characteristics of viable cells by Calc in AM, Calcein AM was uptaken into th retinal ganglion cells and th lev l of xt nsion

of nerve axon of a retinal ganglion cell was observed under a fluorescence microscope. The images of the retinal xtension samples observed under a microscope were dir ctly imported into computer images from the fluorescenc microscope and the length of the nerve axon was measured using an image analyzing soft (MacSCOP, MITANI CO.). The cells having an axon of not less than 100 μm in length were taken as long neurites cells, the cells having an axon of 21 μm - 99 μm wer taken as middle neurites cells, and the cells having an axon of not more than 20 μm in length were taken as short neurites cells (no axonal extension). The proportion (%) of the long neurites cells and middle neurites cells relative to the whole cells was calculated for each.

(2) Results

[0135] The results of the length of the axon of the retinal ganglion cell as measured using an image analyzing soft are shown in Fig. 6.

[0136] The long neurites cells and middle neurites cells of the control group (N=3) were 7% and 12%, respectively. In contrast, the long neurites cells and middle neurites cells of the compound 3 addition group (N=3) were 22% and 23%, respectively; the long neurites cells and middle neurites cells of the compound 4 addition group (N=3) were 11% and 45%, respectively; and the long neurites cells and middle neurites cells of the compound 5 addition group (N=3) were 15% and 53%, respectively. It was confirmed that, as compared to the control group, the test compound addition groups increased long neurites cells and the middle neurites cells for all 3 groups. A significant axonal extension promoting action was confirmed ($P<0.05$) in long neurites cells for the compound 3 addition group and in middle neurites cells for the compound 4 and 5 addition groups, as compared to the control group.

[0137] From the above results, the possibility was suggested that in ganglion cells purely isolated from the retina and cultured, a compound having Rho kinase inhibitory activity is involved in the axon regeneration of the retinal ganglion cells.

Reference Example 1 Production of (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide dihydrochloride 3/2 hydrate

[0138]

(a) To a solution of (R)-4-(1-benzyloxycarbonylaminoethyl)-benzoic acid (1.2 g) in dichloromethane (15 mL) were added thionyl chloride (0.9 mL) and one drop of dimethylformamide, and the mixture was stirred at room temperature for 2 hrs. After the reaction, the solvent was evaporated under reduced pressure to give (R)-4-(1-benzyloxycarbonylaminoethyl)benzoic acid chloride as crystals. Then, the crystals were dissolved in acetonitrile (10 mL) and added dropwise to a solution of 4-amino-1H-pyrrolo[2,3-b]pyridine (240 mg) and diisopropylethylamine (520 mg) in acetonitrile (10 mL), and the mixture was stirred at room temperature for 8 hrs. The precipitated crystals were collected by filtration, dried and dissolved in methanol (7 mL). Sodium methoxide (60 mg) was added and the mixture was stirred at room temperature for 30 min. After the reaction, the mixture was concentrated under reduced pressure. Water was added to the obtained residue and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was evaporated under reduced pressure. The obtained crystals were washed with ethyl acetate to give (R)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-benzyloxycarbonylaminoethyl)benzamide (330 mg).
PMR (DMSO-d_6/TMS) δ: 1.33-1.40 (3H, m), 4.72-4.78 (1H, m), 4.98-5.04 (2H, m), 6.78-6.82 (1H, m), 7.32-8.16 (13H, m)

(b) To a mixture of (R)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-benzyloxycarbonylaminoethyl)benzamide (200 mg), 15% hydrochloric acid-methanol (1 mL) and methanol (6 mL) was added 10% palladium hydroxide carbon (80 mg), and the mixture was stirred under a hydrogen stream at 40°C for 1 hr. After the reaction, the catalyst was filtered off and the residue was concentrated under reduced pressure. The obtained crystals were recrystallized from methanol-ether to give (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide dihydrochloride 3/2 hydrate (120 mg), melting point: 286°C (decomposition).
$[\alpha]_D$=+6.1° (methanol, c=1)
PMR (DMSO-d_6/TMS) δ: 1.54 (3H, d, J=6. 8Hz) , 4. 50-4. 54 (1H, m) , 7.11 (1H, br), 7.55 (1H, br), 7.70 (2H, d, J=8.3Hz), 8.02-8.06 (3H, m) , 8.33 (1H, br) , 8.62 (3H, br) , 10.99 (1H, br)

Reference Example 2 Production of (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride

[0139]

(a) (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide dihydrochloride 3/2 hydrate (8.5 g) ob-

tained in Reference Example 1 was dissolved in water (50 mL) and 1N-NaOH aqueous solution was added dropwise while stirring under ice-cooling. The precipitated crystals were collected by filtration and dried (warm air: 60°C, 10 hrs) to give a free base form (6.2 g).

mp. 210-212°C

EA: calcd. for $C_{16}H_{16}N_4O$: C;68.55, H; 5.75, N; 19.99 found C;68.58, H; 5.70, N; 19.81

^{1}H-NMR (DMSO-d_6) δ: 1. 29 (3H, d, J=8.0Hz), 1.88 (2H, bs), 4. 09 (1H, m), 6.80 (1H, s), 7.33 (1H, s), 7.53 (2H, d, J=7.8Hz), 7.70 (1H, d, J=7.8Hz), 7.92 (2H, d, J=7.8Hz), 8.14 (1H, d, J=7.8Hz), 10.26 (1H, bs) , 11.57 (1H, bs)

$[\alpha]_D$=+14.7° (methanol, c=0.5)

(b) To the free base form (2.8 g) obtained in the above-mentioned (a) was added ethanol (5 mL), and 1N hydrochloric acid (10 mL) was added while heating to 60°C. After dissolution, the mixture was filtered while it was hot and stirred at room temperature for 2 hrs and in an ice-salt bath for 1.5 hrs. The precipitated crystals were collected by filtration, dried (warm air: 60°C, 10 hrs) and H_2O-EtOH (2/1) (20 mL) was added. After dissolving under reflux, the mixture was filtered while it was hot and stirred at room temperature for 2 hrs and in an ice-salt bath for 1.5 hrs. Thereafter, the crystals were collected by filtration and dried (warm air: 60°C, 24 hrs) to give (R)-(+)-N-(1H-pyrrolo[2,3-b] pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride (2.4 g).

mp. 298°C (decomposition)

EA: calcd. for $C_{16}H_{16}N_4O$·1HCl C;60.66, H; 5.41, N; 17.69 found C; 60.56, H; 5.32, N; 17.62

^{1}H-NMR(DMSO-d_6)δ: 1.58 (3H, d, J=8.0Hz), 4.51 (1H, m), 6.80 (1H, s) , 7.35 (1H, s) , 7.70 (3H, m) , 8.05 (2H, d, J=7. 8Hz) , 8.15 (1H, d, J=7.8Hz), 8.68 (3H, bs), 10.41 (1H, bs), 11.60 (1H, bs) $[\alpha]_D$=+8.2° (methanol, c=1.0)

Industrial Field of Utilization

[0140] Since compounds 1 to 5 have axon of the retinal ganglion cell extending action and optic nerve cell regenerating action, a compound having Rho kinase inhibitory activity is considered to improve visual function disorders caused by damage, degeneration and the like of the retinal nerve and the optic nerve. Accordingly, a compound having Rho kinase inhibitory activity is considered to be effective for the improvement of visual function in a visual disorder caused by damage due to retinal inflammation and the like (retinal neuropathy, retinal vascular occlusion, periphlebitis retinae, Eales' disease, ischemic ophthalmopathy, retinal arteriolar microaneurysm, retinopathy caused by hypertension, renal disease and blood disease, diabetic retinopathy, retinal dystrophy, macular dystrophy, chorioretinopathy, macular degeneration, macular edema, retinal pigment epithelium detachment, degenerative retinoschisis, retinoblastoma, retinal pigment epithelioma etc.) and the like; improvement of visual function in a visual disorder caused by degeneration, damage of the optic nerve (optic neuritis, capillary angioma of optic disc, ischemic optic neuropathy, defects of retinal nerve fibers layer, retinal optic atrophy, neurotmesis of optic nerve, traumatic optic neuropathy, choked disc, coloboma of optic disc, optic nerve hypoplasia, toxic optic atrophy etc.); improvement of visual function in a visual disorder due to optic atrophy, degeneration and the like caused by elevated intraocular pressure (glaucoma etc.) and the like; and further, proliferation and functional maintenance of visual cells including retinal ganglion cells in retinal transplantation as well as regeneration of optic nerve in optic nerve transplantation.

[0141] This application is based on patent application Nos. 2001-113329 and 2001-308010 filed in Japan, the contents of which are all hereby incorporated by reference.

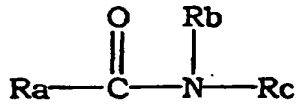
Claims

1. A visual function disorder improving agent that improves a visual function disorder caused by damage or degeneration of retinal nerve cell or optic nerve, which comprises a compound having Rho kinase inhibitory activity.

2. The agent of claim 1, wherein the improvement of the visual function disorder is by way of promotion of extension of axon of a retinal ganglion cell.

3. The agent of claim 1, wherein the improvement of the visual function disorder is by way of regeneration of an optic nerve cell.

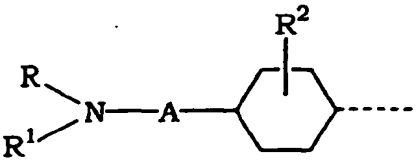
4. The agent of any of claims 1 to 3, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



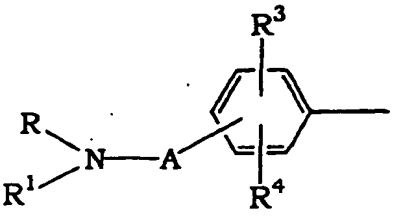
(I)

wherein

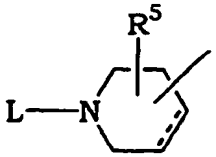
Ra is a group of the formula



(a)



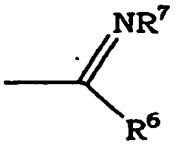
(b)



(c)

in the formulas (a) and (b),

R is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



(d)

wherein R^6 is hydrogen, alkyl or formula:-NR^8R^9 wherein R^8 and R^9 are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R^7 is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R^6 and R^7 in combination show a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

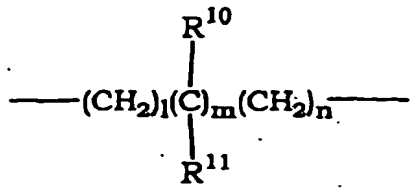
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or

R and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and

A is a group of the formula

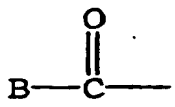


(e)

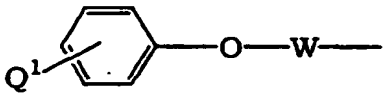
wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

in the formula (c),

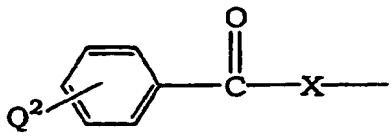
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



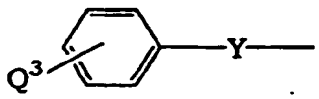
(f)



(g)



(h)



(i)

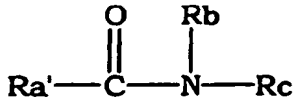
wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,
Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,
W is alkylene,
Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,
X is alkylene,
Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl; and
Y is a single bond, alkylene or alkenylene, and

in the formula (c),
a bond denoted by a broken line and a solid line

is a single bond or a double bond;
R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

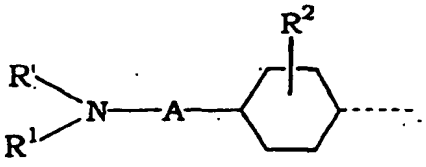
5. The agent of any of claims 1 to 3, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



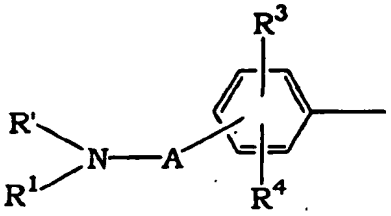
(I')

wherein

Ra' is a group of the formula



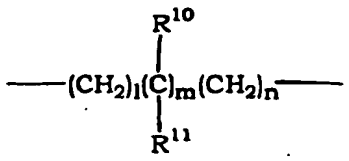
(a')



(b')

wherein

R'	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,
R^1	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or
R' and R^1	in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,
R^2	is hydrogen or alkyl,
R^3 and R^4	are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and
A	is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb	is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc	is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

6. The agent of any of claims 1 to 3, wher in the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)b nzamid or a pharmaceutically acc ptable acid addition salt th reof, or a prodrug thereof.

7. The agent of any of claims 1 to 3, wher in the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochlorlde.

8. The agent of any of claims 1 to 3, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

9. An agent for promoting extension of axon of a retinal ganglion cell, which comprises a compound having Rho kinase inhibitory activity as an effective component.

10. The agent of claim 9, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 4, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

11. The agent of claim 9, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 5, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

12. The agent of claim 9, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

13. The agent of claim 9, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

14. The agent of claim 9, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

15. An agent for promoting regeneration of an optic nerve cell, which comprises a compound having Rho kinase inhibitory activity as an effective component.

16. The agent of claim 15, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 4, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

17. The agent of claim 15, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 5, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

18. The agent of claim 15, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

19. The agent of claim 15, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

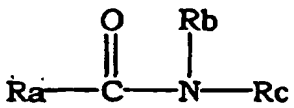
20. The agent of claim 15, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition for improving a visual function disorder, which comprises a compound having Rho kinase inhibitory activity and a carrier acceptable for formulation of a preparation, which improves a visual function disorder caused by damage or d g neration of r tinal nerve cell or optic nerve.

22. The pharmaceutical composition of claim 21, wherein the improvement of th visual function disorder is by way of promotion of xtension of axon of a r tinal ganglion cell.

23. The pharmaceutical composition of claim 21, wherein the improvement of the visual function disorder is by way of regeneration of an optic nerv cell.

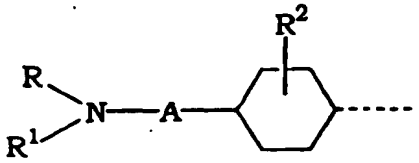
24. The pharmaceutical composition of any of claims 21 to 23, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



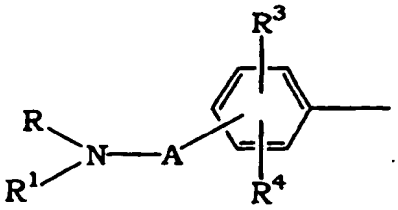
(I)

wherein

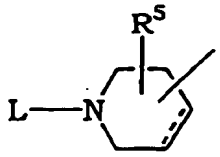
Ra is a group of the formula



(a)



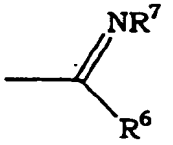
(b)



(c)

in the formulas (a) and (b),

R is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



(d)

wherein R^6 is hydrogen, alkyl or formula: $-NR^8R^9$
wherein R^8 and R^9 are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R^7 is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R^6 and R^7 in combination show a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^1 Is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or

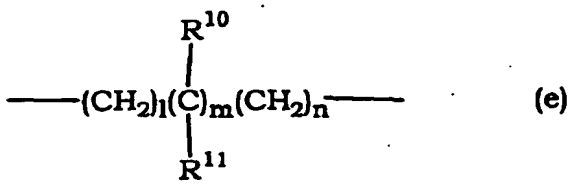
R and R^1 in combination form, together with th adjacent nitrogen atom, a group forming a heterocycle option-

ally furth r having, in the ring, oxyg n atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrog n or alkyl,

R^3 and R^4 ar the same or diff r nt and each is hydrogen, alkyl, aralkyl, halog n, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, m rcapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and

A is a group of the formula

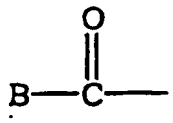


(e)

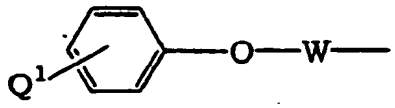
wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

in the formula (c),

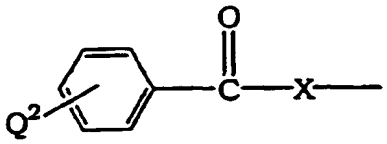
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



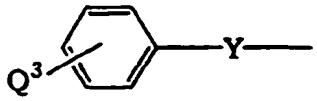
(f)



(g)



(h)



(i)

wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,

W is alkylene,

Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl; and

Y is a single bond, alkylene or alkenylene, and in the formula (c),

a bond denoted by a broken line and a solid line

is a single bond or a double bond;

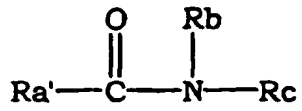
R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isom r th reof and/or a pharmaceutically acceptable acid addition salt th reof, or a pr drug th reof.

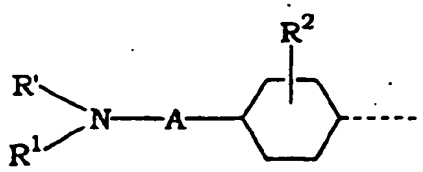
25. The pharmaceutical composition of any of claims 21 to 23, wherein th compound having a Rho kinas inhibitory activity is an amide compound of th following formula (I')



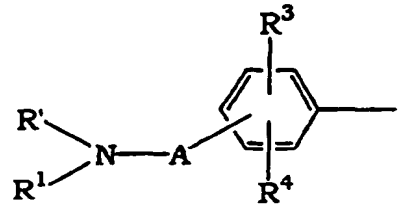
(I')

wherein

Ra' is a group of the formula



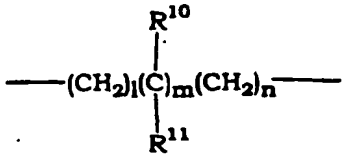
(a')



(b')

wherein

R'	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,
R^1	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or
R' and R^1	in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,
R^2	is hydrogen or alkyl,
R^3 and R^4	are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and
A	is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb	is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc	is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

26. The pharmaceutical composition of any of claims 21 to 23, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

27. The pharmaceutical composition of any of claims 21 to 23, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

28. The pharmaceutical composition of any of claims 21 to 23, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition for promoting extension of axon of a retinal ganglion cell, which comprises a compound having Rho kinase inhibitory activity and a carrier acceptable for formulation of a preparation.

30. The pharmaceutical composition of claim 29, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 24, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

31. The pharmaceutical composition of claim 29, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 25, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

32. The pharmaceutical composition of claim 29, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

33. The pharmaceutical composition of claim 29, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

34. The pharmaceutical composition of claim 29, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition for promoting regeneration of an optic nerve cell, which comprises a compound having Rho kinase inhibitory activity and a carrier acceptable for formulation of a preparation.

36. The pharmaceutical composition of claim 35, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 24, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

37. The pharmaceutical composition of claim 35, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 25, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

38. The pharmaceutical composition of claim 35, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

39. The pharmaceutical composition of claim 35, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

40. The pharmaceutical composition of claim 35, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

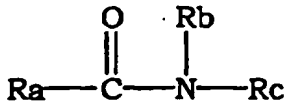
41. A method of improving a visual function disorder caused by damage or degeneration of retinal nerve cell or optic

nerve, which comprises administ ring an effective amount of a compound having Rho kinase inhibitory activity to a patient.

42. The method of claim 41, wherein the improvement of the visual function disorder is by way of promotion of extension of axon of a retinal ganglion cell.

43. The method of claim 41, wherein the improvement of the visual function disorder is by way of regeneration of an optic nerve cell.

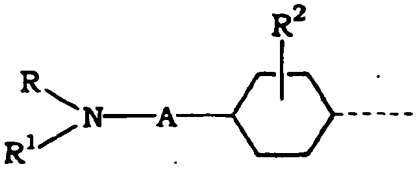
44. The method of any of claims 41 to 43, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



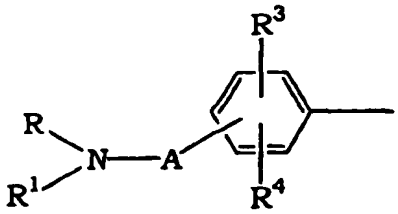
(I)

wherein

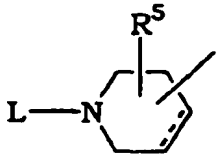
Ra is a group of the formula



(a)



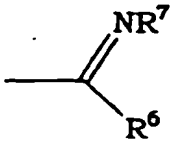
(b)



(c)

in the formulas (a) and (b),

R is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



(d)

wherein R^6 is hydrogen, alkyl or formula:-NR^8R^9
wherein R^8 and R^9 are the same or different and each is hydrogen, alkyl, aralkyl or phenyl, R^7 is hydrogen, alkyl, aralkyl, phenyl, nitro or cyano, or R^6 and R^7 in combination show a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

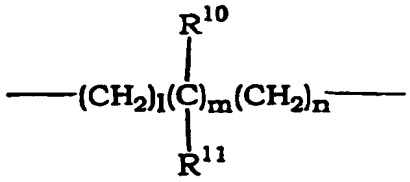
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or

R and R^1 in combination form, together with th adjacent nitrogen atom, a group forming a heterocycle optionally furth r having, in th ring, oxyg n atom, sulfur atom or optionally substitut d nitrog n atom,

R^2 is hydrog n or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and

A is a group of the formula

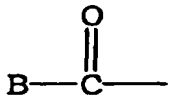


(c)

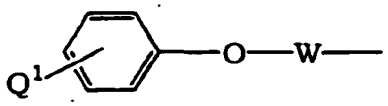
wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3 ,

in the formula (c),

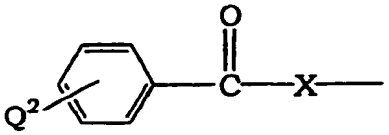
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



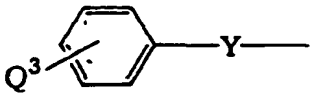
(f)



(g)



(h)



(i)

wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,

W is alkylene,

Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl; and

Y is a single bond, alkylene or alkenylene, and in the formula (c),

a bond denoted by a broken line and a solid line

is a single bond or a double bond;

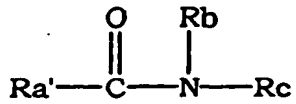
R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmac utically acceptable acid addition salt thereof, or a prodrug thereof.

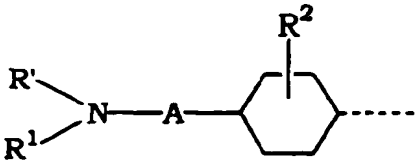
45. The method of any of claims 41 to 43, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



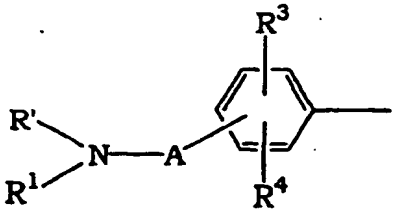
(I')

wherein

Ra' Is a group of the formula



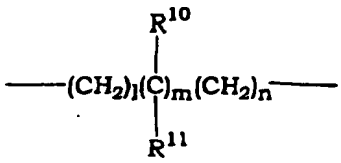
(a')



(b')

wherein

R'	is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,
R^1	Is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or
R' and R^1	in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,
R^2	is hydrogen or alkyl,
R^3 and R^4	are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and
A	is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and ach is hydrogen, alkyl, haloalkyl, aralkyl, hy-

droxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substitut d heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

46. The method of any of claims 41 to 43, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

47. The method of any of claims 41 to 43, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

48. The method of any of claims 41 to 43, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

49. A method of promoting extension of axon of a retinal ganglion cell, which comprises administering an effective amount of a compound having Rho kinase inhibitory activity to a patient.

50. The method of claim 49, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 44, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

51. The method of claim 49, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 45, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

52. The method of claim 49, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

53. The method of claim 49, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

54. The method of claim 49, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

55. A method of promoting regeneration of an optic nerve cell, which comprises administering an effective amount of a compound having Rho kinase inhibitory activity to a patient.

56. The method of claim 55, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 44, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

57. The method of claim 55, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 45, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

58. The method of claim 55, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

59. The method of claim 55, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

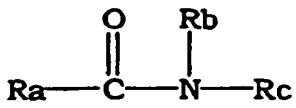
60. The method of claim 55, wherein the compound having Rho kinas inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylb nzene derivativ s and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

61. Use of a compound having Rho kinase inhibitory activity for th production of an agent for improving a visual function disorder, which improves a visual function disorder caused by damage or degeneration of retinal nerve cell or optic nerve.

62. The use of claim 61, wherein the improvement of the visual function disorder is by way of promotion of extension of axon of a retinal ganglion cell.

63. The use of claim 61, wherein the improvement of the visual function disorder is by way of regeneration of an optic nerve cell.

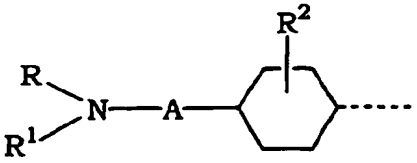
64. The use of any of claims 61 to 63, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I)



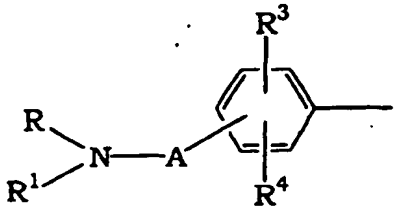
(I)

wherein

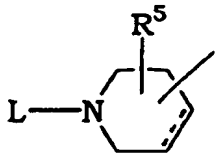
Ra is a group of the formula



(a)



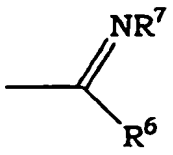
(b)



(c)

in the formulas (a) and (b),

R is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or a group of the formula



(d)

wherein R^6 is hydrogen, alkyl or formula:-NR^8R^9 wher in R^8 and R^9 are th same or different and ach is hydrogen, alkyl, aralkyl or ph nyl, R^7 is hydrog n, alkyl, aralkyl, ph nyl, nitro or cyano, or R^6 and R^7 in combination show a group forming a het rocycl optionally further having, in the ring, oxyg n atom, sulfur atom or optionally substituted nitrog n atom,

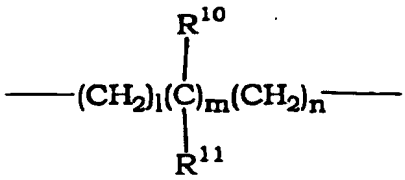
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substitu nt on the ring, or

R and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

R^2 is hydrogen or alkyl,

R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and

A is a group of the formula

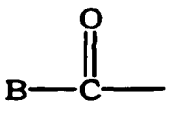


(e)

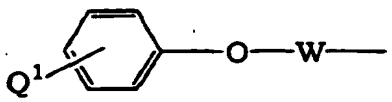
wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

in the formula (c),

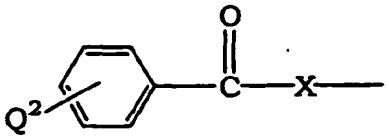
L is hydrogen, alkyl, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



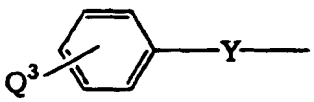
(f)



(g)



(h)



(i)

wherein B is hydrogen, alkyl, alkoxy, aralkyl, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,

Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,

W is alkylene,

Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,

X is alkylene,

Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl; and

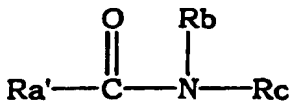
Y is a single bond, alkylene or alkenylene, and in the formula (c), .

a bond denoted by a brok n lin and a solid line

is a single bond or a doubl bond;
R^5 is hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

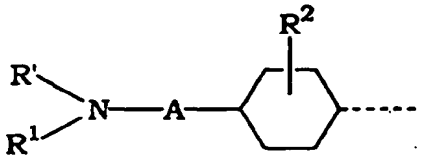
65. The use of any of claims 61 to 63, wherein the compound having a Rho kinase inhibitory activity is an amide compound of the following formula (I')



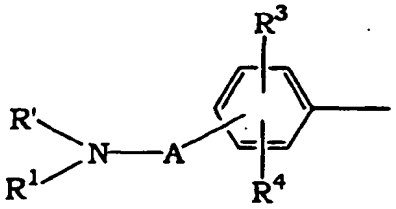
(I')

wherein

Ra' is a group of the formula



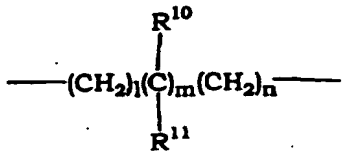
(a')



(b')

wherein

R' is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring,
R^1 is hydrogen, alkyl, or cycloalkyl, cycloalkylalkyl, phenyl or aralkyl, which optionally has a substituent on the ring, or
R' and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally further having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,
R^2 is hydrogen or alkyl,
R^3 and R^4 are the same or different and each is hydrogen, alkyl, aralkyl, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, mono- or dialkylcarbamoyl or azide, and
A is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, haloalkyl, aralkyl, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination and l, m and n are each 0 or an integer of 1-3,

Rb is a hydrogen, an alkyl, an aralkyl, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen,

an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

66. The use of any of claims 61 to 63, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

67. The use of any of claims 61 to 63, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

68. The use of any of claims 61 to 63, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

69. Use of a compound having Rho kinase inhibitory activity for the production of an agent for promoting extension of axon of a retinal ganglion cell.

70. The use of claim 69, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 64, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

71. The use of claim 69, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 65, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

72. The use of claim 69, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

73. The use of claim 69, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

74. The use of claim 69, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

75. Use of a compound having Rho kinase inhibitory activity for the production of an agent for promoting the regeneration of an optic nerve cell.

76. The use of claim 75, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I) described in claim 64, an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

77. The use of claim 75, wherein the compound having Rho kinase inhibitory activity is an amide compound represented by the formula (I') described in claim 65, an isomer thereof and/or a pharmaceutically acceptable acid

addition salt thereof, or a prodrug ther of.

78. The use of claim 75, wher in the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b] pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof, or a prodrug thereof.

79. The use of claim 75, wherein the compound having Rho kinase inhibitory activity is (R)-(+)-N-(1H-pyrrolo[2,3-b] pyridin-4-yl)-4-(1-aminoethyl)benzamide monohydrochloride.

80. The use of claim 75, wherein the compound having Rho kinase inhibitory activity is a compound selected from thiochroman compounds, isoquinolinesulfonamide derivatives, vinylbenzene derivatives and ethacrynic acid, or a pharmaceutically acceptable salt thereof.

81. A commercial package comprising the pharmaceutical composition for improving a visual function disorder of any of claims 21 to 28 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for improving a visual function disorder caused by damage or degeneration of retinal nerve cell or optic nerve.

FIG. 1

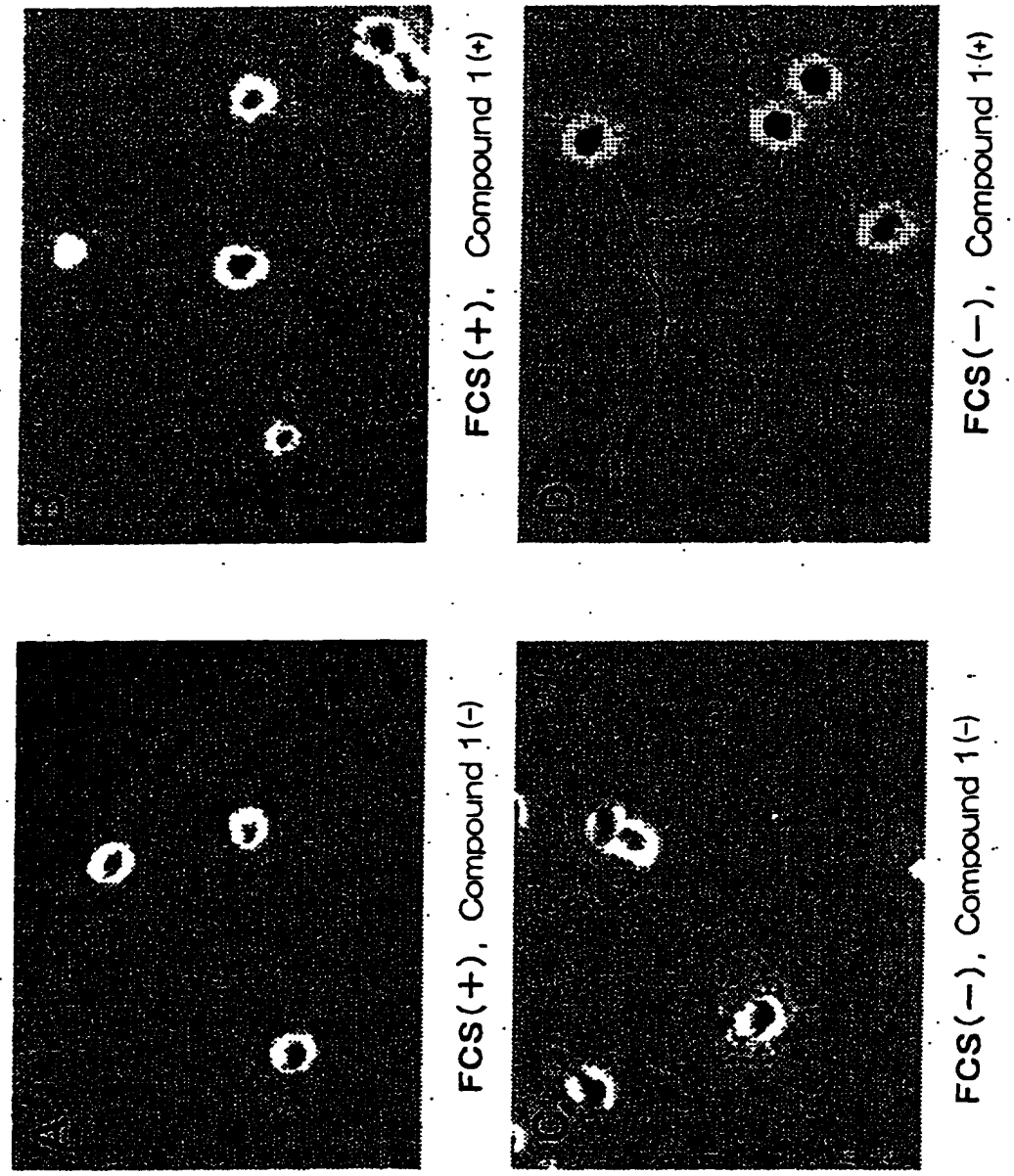


FIG. 2

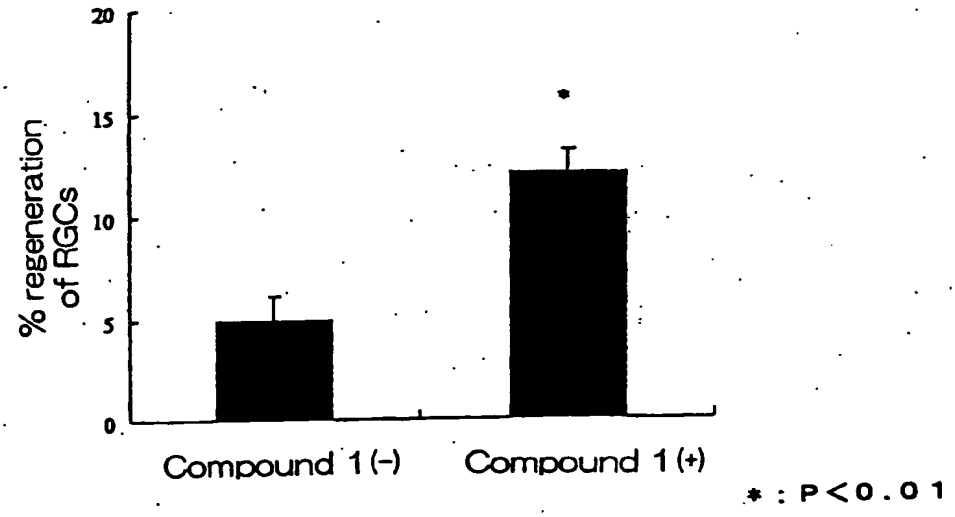
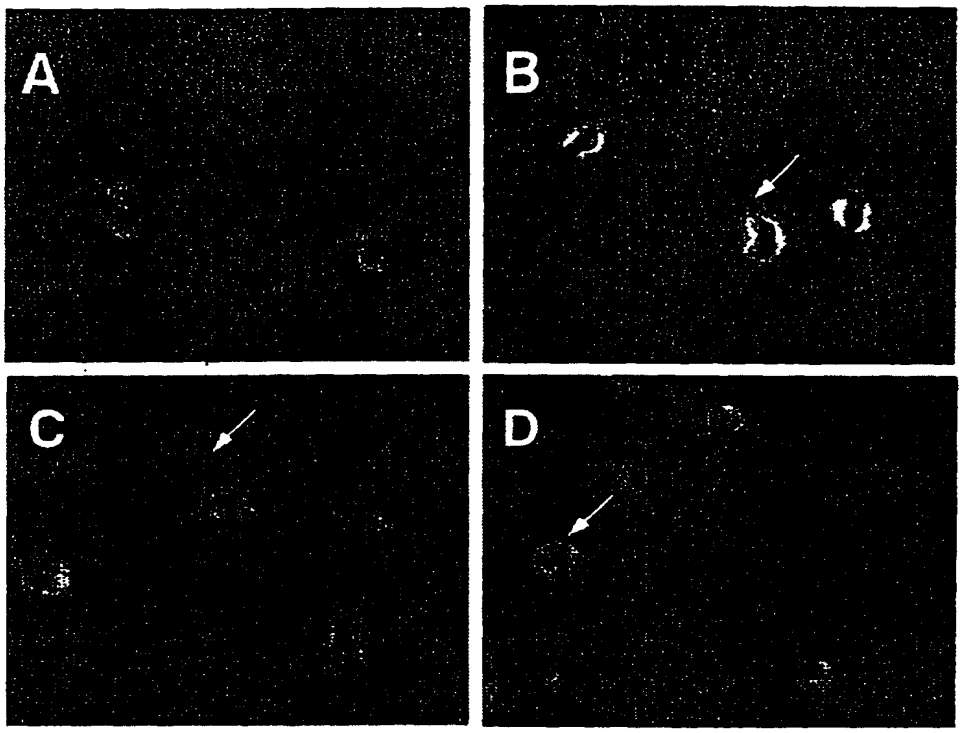


FIG. 3



A : FCS (+), Compound 2 (−)

B : FCS (−), Compound 2 (−)

C : FCS (−), Compound 2 (+)

D : FCS (−), Compound 2 (−), LPA (+)

FIG. 4

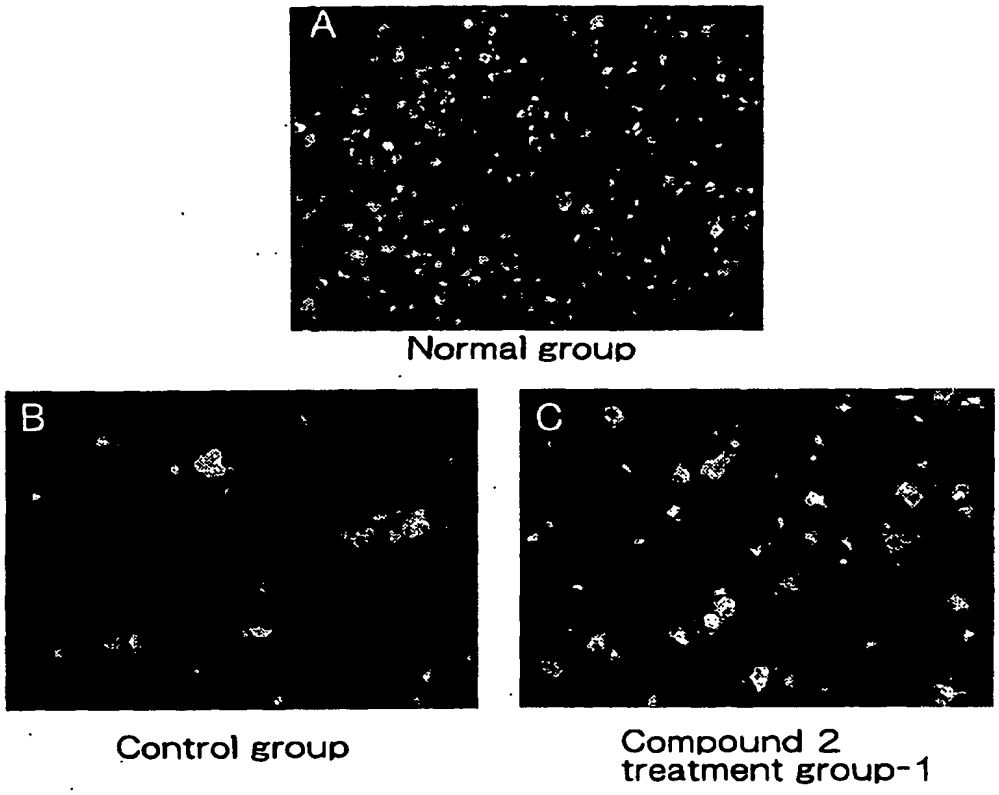

A
Normal group
B
Control group
C
Compound 2
treatment group-1

FIG. 5

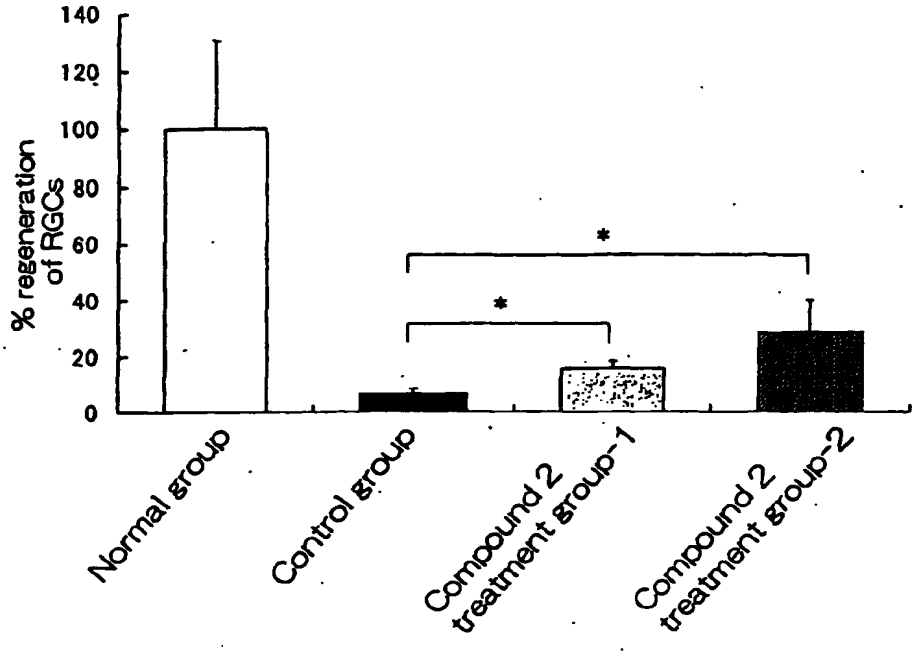
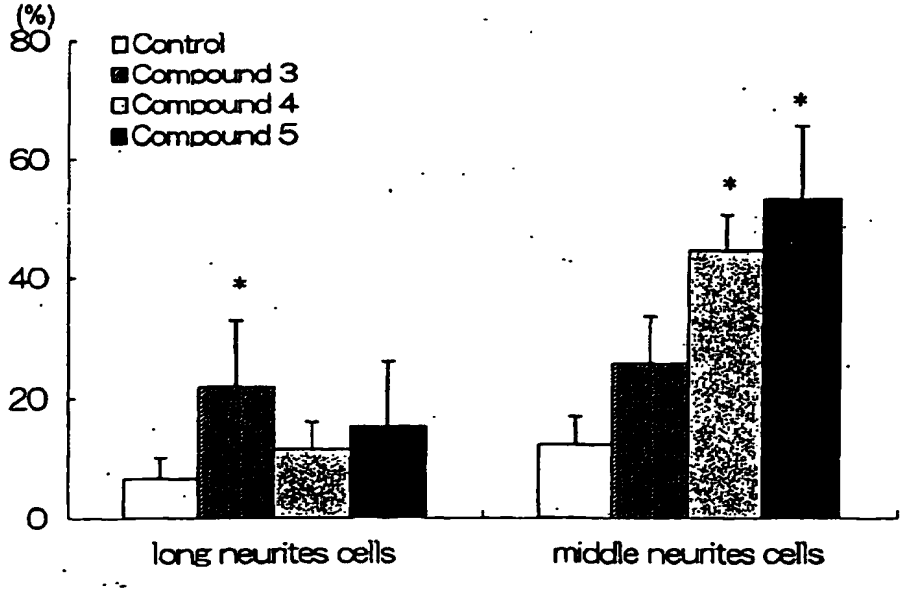

140
120
100
80
60
40
20
0
% regeneration of RGCs
*
*
Normal group
Control group
Compound 2 treatment group-1
Compound 2 treatment group-2

FIG. 6


(%)
80
60
40
20
0
Control
Compound 3
Compound 4
Compound 5
*
*
*
long neurites cells
middle neurites cells

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/03590

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K45/00, 31/16, 31/337, 31/415, 31/437, 31/4375, 31/44, 31/4409, 31/4439, 31/444, 31/4545, 31/50, 31/505, 31/519, 31/52, A61P25/00, 27/02, 43/00//C07D213/75, 213/79, 213/82, 213/89, 231/40,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K45/00-45/08, 31/00-31/80, A61P1/00-43/00, C07D213/00-213/89, 231/00-231/40, 237/00-237/20, 239/00-239/50, 401/00-401/14, 405/00-405/14, 409/00-409/14, 471/00-471/04, 487/00-487/04,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE(STN), CAPLUS(STN), EMBASE(STN), BIOSIS(STN), BIOTECHABS(STN), JMEDICINE(JOIS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HIROSE, M. et al., Molecular Dissection of the Rho-associated Protein Kinase(p160ROCK)-regulated Neurite Remodeling in Neuroblastoma N1E-115 Cells. J. Cell Biol., 1998, 141(7), pages 1625 to 1636, full text	1-40,61-81
Y	LEHAMANN, M., et al., Inactivation of Rho Signaling Pathway Promotes CNS Axon Regeneration. J. Neurosci., 1999, 19(17), pages 7537 to 7547, full text	1-40,61-81
Y	BITO, H. et al., A critical role for a Rho-associated kinase, p160ROCK, in determining axon outgrowth in mammalian CNS neurons. Neuron, 2000, 26(2), pages 431 to 441, full text	1-40,61-81

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 May, 2002 (28.05.02)	11 June, 2002 (11.06.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/03590

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/19694 A1 (Amgen Inc.), 05 June, 1997 (05.06.97), Claims; Background of the Invention & JP 2000-502057 A & US 564175 A & US 5736516 A & EP 863766 A1 & AU 9710592 A & NO 9802275 A & HU 9802374 A2 & BR 9611750 A & CN 12035832 A & CZ 9801544 A3 & SK 9800659 A3 & MX 9803993 A1 & KR 99071540 A	1-40,61-81
Y	WO 98/34485 A1 (Layton Bioscience, Inc.), 13 August, 1998 (13.08.98), Claims & JP 2001-511788 A & EP 1018884 A1 & US 6162428 A	1-40,61-81
Y	WO 99/00133 A1 (Merck & Co., Inc.), 07 January, 1999 (07.01.99), Full text & JP 2002-506401 A & EP 1024810 A1 & AU 9881622 A	1-40,61-81
Y	WO 98/06433 A1 (Yoshitomi Pharmaceutical Industries, Ltd.), 19 February, 1998 (19.02.98), Claims & EP 956865 A1 & US 62188410 B1 & US 2002/0032148 A1 & AU 9737851 A & AU 200157778 A & NO 9900622 A & CZ 9900460 A3 & BR 9711154 A & MX 9901475 A1 & CN 1233188 A & KR 2000029918 A & HU 9903694 A2 & NZ 334613 A	1-40,61-81
Y	EP 1034793 A1 (Senju Pharmaceutical Co., Ltd.), 13 September, 2000 (13.09.00), Full text & WO 00/09162 A1 & AU 9951981 A & CN 1287494 A & KR 2001015761 A	1-40,61-81
Y	EP 1064944 A1 (Schering AG.), 03 January, 2001 (03.01.01), Full text (Family: none)	1-3,8,9,14, 15,20-23,28, 29,34,35,40, 61-63,68,69, 74,75,80,81
Y	JP 10-201480 A (Kirin Brewery Co., Ltd.), 04 August, 1998 (04.08.98), Claims; Par. Nos. [0082] to [0112] (Family: none)	1-3,9,15, 21-23,29,35, 61-63,69,75, 81

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/03590

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 10-113187 A (Kirin Brewery Co., Ltd.), 06 May, 1998 (06.05.98), Claims; Par. Nos. [0089] to [0108] & US 5906819 A	1-3,9,15, 21-23,29,35, 61-63,69,75, 81
A	WO 00/57914 A1 (Santen Pharmaceutical Co., Ltd.), 05 October, 2000 (05.10.00), & JP 2000-336042 A & AU 200033286 A	1-40,61-81
A	JP 2001-81048 A (Wakamoto Pharmaceutical Co., Ltd.), 27 March, 2001 (27.03.01), (Family: none)	1-40,61-81
A	EP 728480 A1 (Rhoto Pharmaceutical Co., Ltd.), 28 August, 1986 (28.08.86), & JP 8-231400 A	1-40,61-81
A	WO 99/23113 A2 (McKERRACHER, Lisa), 14 May, 1999 (14.05.99), & EP 1049715 A2 & AU 9897321 A & CA 2214841 A1	1-40,61-81
A	EP 609822 A1 (Takeda Chemical Industries, Ltd.), 10 August, 1994 (10.08.94), Page 2, line 8 to page 3, last line & JP 6-287139 A & US 5665769 A & CA 2114694 A & CN 1099611 A & TW 325997 A	1-40,61-81
P,A	McKERRACHER, L., Strategies to promote regeneration of adult rat retinal ganglion cell axons in the nerve. Bulletin of the Japanese Society for Neurochemistry, 01 September, 2001 (01.09.01), 4(2/3), page 253(S47-6)	1-40,61-81

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/03590

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

Int.Cl[7] 237/20, 239/42, 239/48, 239/50, 401/12, 401/14, 405/14, 409/14, 471/04, 487/04, 495/04

(According to International Patent Classification (IPC) or to both national classification and IPC)

Continuation of B. FIELDS SEARCHED
Minimum Documentation Searched(International Patent Classification (IPC))

Int.Cl[7] 495/00-495/04

Minimum documentation searched (classification system followed by classification symbols)

Form PCT/ISA/210 (extra sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/03590

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 41-60
because they relate to subject matter not required to be searched by this Authority, namely:
The inventions as set forth in claims 41 to 60 pertain to methods for treatment of the human body by therapy (Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)